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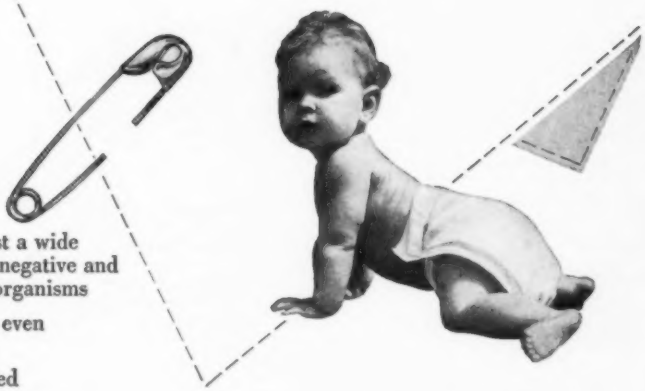

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The Journal of Pediatrics

VOL. 43 NOVEMBER, 1953 No. 5

THE DEVELOPING FUNDUS OCULI OF THE PREMATURE INFANT AND ITS RELATIONSHIP TO RETROLENTAL FIBROPLASIA

MARY CRITZ FLETCHER, M.D.
HOUSTON, TEXAS

EXAMINATIONS of the fundi of premature infants were begun at Jefferson Davis Hospital in April, 1950. At the same time an attempt was made to locate children in the community with residual lesions of retrolental fibroplasia. One hundred seventeen graduates of this premature nursery were located and examined for retrolental fibroplasia (RLF) and no lesions were found. Although this survey was not complete, it did suggest that RLF was not common in prematurely born infants discharged from this nursery prior to 1950. It is interesting that the first appearance of this disease coincided with the establishment of a modern, separate, well-equipped premature unit, and improvement in survival rate. (See Table I.)

Since April, 1950, periodic examinations of the fundi of premature infants have been made. These examinations were begun shortly after birth and continued weekly or fortnightly during their hospital stay, and monthly when possible until 6 months of age. All examinations were done by direct ophthalmoscopy, using a small lid retractor, without anesthesia and without depression of the globe. Fresh atropine 1:5,000 was found to be a satisfactory mydriatic.

From April, 1950, to January, 1953, a total of 320 premature infants were examined serially, 270 at Jefferson Davis Hospital and 50 private patients in the Houston area. Of the 320 infants, 223 weighed less than 1,700 grams and 97 weighed between 1,701 and 2,500 grams at birth. From these examinations, observations of the development of the premature fundus and the clinical appearance of RLF in the fundi of the eyes of prematurely born infants have been made. These observations are reported in this paper.

Serial examinations from birth of 320 small premature infants have revealed a definite pattern of growth and development of the eye which is schematically presented in Diagram 1. About half of infants with birth weights less than 1,500 grams and the majority of those with birth weights less than 1,250 grams are born with an "immature fundus" which tends to remain unchanged for several weeks. A critical period of differentiation and maturation is then reached rapidly so that within one to two weeks the retina attains the features seen in the "mature" full-term eye. In this study, 177 infants were examined within the first two weeks of life. The fundi have been

From The Department of Pediatrics, Baylor University College of Medicine, and The Premature Service, Jefferson Davis Hospital.

TABLE I. PREMATURE MORTALITY STATISTICS, 1947 TO 1953, JEFFERSON DAVIS HOSPITAL, HOUSTON, TEXAS. THE DEATHS REPORTED INCLUDE ALL INFANT DEATHS UP TO THE TIME OF DISMISSAL FROM THE NURSERY

	1947			1948			1949			1950			1951			1952		
GRAMS	NO. BORN	NO. DIED	% MORT.	NO. BORN	NO. DIED	% MORT.	NO. BORN	NO. DIED	% MORT.	NO. BORN	NO. DIED	% MORT.	NO. BORN	NO. DIED	% MORT.	NO. BORN	NO. DIED	% MORT.
2,001-2,500	58	15	26	121	20	17	216	4	2	204	8	4	215	4	2	204	9	4
1,501-2,000	50	19	38	53	30	57	61	8	13	88	9	10	106	13	12	108	17	16
1,001-1,500	19	16	84	42	32	76	31	19	61	46	22	48	53	18	34	62	33	53
Less than 1,000	17	17	100	29	29	100	23	23	100	52	49	94	51	48	94	51	48	94
Unknown	14	14	100	9	9	100	1	1	100	1	1	100	0	0	0	0	0	0
Total	158	81	51	254	120	47	332	55	17	391	89	23	425	83	20	425	107	25

classified as "immature," "transitional," and "mature." The incidences of the three degrees of maturation in the various weight groups at birth are shown in Table II. No infants weighing less than 1,000 grams at birth showed mature fundi, approximately 50 per cent of those weighing 1,500 grams had mature fundi, and all of those above 2,000 grams had mature fundi. (See Graph 1.)

The time required to attain this maturation varies with the birth weight. The smaller baby tends to retain immature features for a longer period of time than does the larger baby. In this series, infants weighing less than 1,000 grams required an average of

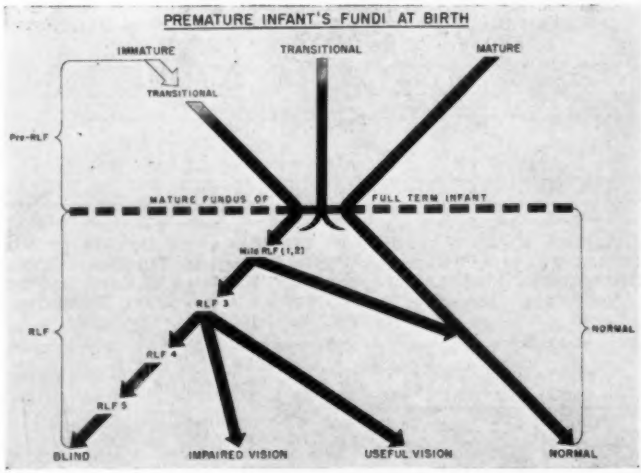
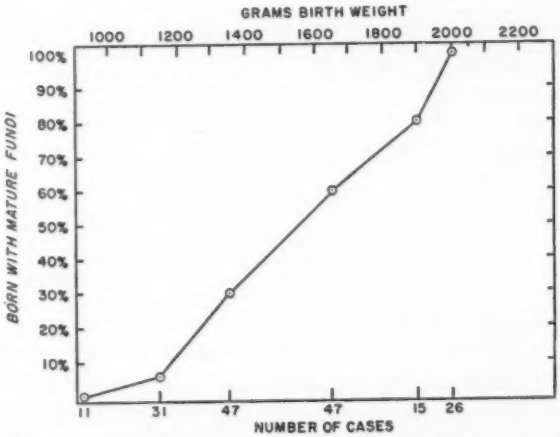


Diagram 1.—Schematic presentation of the development of the premature infant's fundus.



Graph 1.—Per cent incidence *of mature* fundi seen at birth (0 to 14 days) in 177 premature infants of various weight groups.

forty-three days and those weighing 1,500 to 1,750 grams, an average of nine days to begin maturation. The pattern of development of the fundus is more closely allied with weight than with age. (Compare Tables III and IV. Refer to Table XV.)

TABLE II. INCIDENCE OF IMMATURE, TRANSITIONAL, AND MATURE FUNDI IN 177 PREMATURE INFANTS OF VARIOUS BIRTH WEIGHTS, EXAMINED WITHIN 0 TO 14 DAYS AFTER BIRTH. SEX AND RACE DISTRIBUTION IS NEARLY EQUAL

BIRTH WT.	<1,000		1,001-1,250		1,251-1,500		1,501-1,750		1,751-2,000		>2,000	
FUNDUS	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Immature	11	100	26	84	21	45	9	19	0	0	0	0
Transitional	0	0	4	13	12	26	10	21	3	20	0	0
Mature	0	0	1	3	14	29	28	60	12	80	26	100
Total	11	100	31	100	47	100	47	100	15	100	26	100

TABLE III. AVERAGE WEIGHTS ATTAINED BY 245 PREMATURE INFANTS OF VARIOUS BIRTH WEIGHT GROUPS DURING WHICH THE FUNDI PROGRESSED THROUGH THE STAGES OF PRERETROLENTAL FIBROPLASIA, ACUTE RLF, RESIDUAL RLF, OR RETURN TO NORMALITY (JEFFERSON DAVIS HOSPITAL AND PRIVATE NURSERIES OF HOUSTON, 1950-1953)

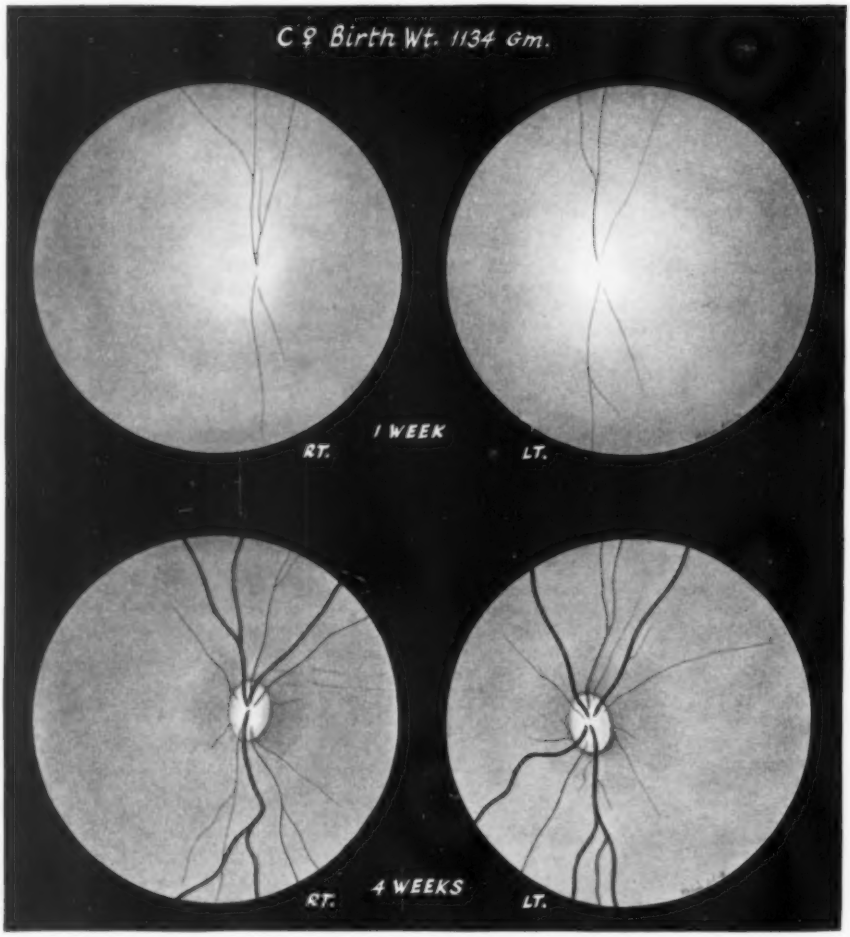
BIRTH WEIGHT GRAMS	TRANSITIONAL	MATURE	RLF 1	RLF 2	RLF 3	RLF 4	RESIDUAL SCARRING	RETURN TO NORMAL
2,001-2,500				All Mature.	No RLF			
1,751-2,000	1,960	1,970	2,300					3,000
1,501-1,750	1,600	1,670	2,020	2,150	2,800	3,300	3,000	2,250
1,251-1,500	1,490	1,580	1,960	1,910	1,900	4,100	4,000	3,600
1,001-1,250	1,260	1,410	1,700	1,990	2,080	2,760	3,160	2,530
<1,000	1,310	1,440	1,825	2,000	2,070		3,000	2,200

TABLE IV. AVERAGE DAYS OF LIFE OF 245 PREMATURE INFANTS OF VARIOUS BIRTH WEIGHT GROUPS DURING WHICH THE FUNDI PROGRESSED THROUGH THE STAGES OF PRERETROLENTAL FIBROPLASIA, ACUTE RETROLENTAL FIBROPLASIA, RESIDUAL RLF, OR RETURN TO NORMAL

BIRTH WEIGHT GRAMS	TRANSITIONAL	MATURE	RLF 1	RLF 2	RLF 3	RLF 4	RESIDUAL SCARRING	RETURN TO NORMAL
2,001-2,500				All Mature.	No RLF			
1,751-2,000	7	8	31					50
1,501-1,750	9	13	42	47	51	77	114	75
1,250-1,500	15	20	51	40	40	81	150	71
1,001-1,250	23	34	45	58	62	90	144	85
<1,000	43	51	63	93	102		150	91

A. *The Immature Fundus.*—The immature fundus is obscured by a vitreous haze or clouding which may prevent visualization of the disc, blood vessels, and hyaloid remnants. However, faint blood vessel outlines are usually visible. (See Plates I and II.) The disc is oval with indistinct margins. When vessels are seen they are quite small, usually two in number, emerging from the superior and inferior poles of the disc. Sharp focus is rarely obtained but the disc is best seen at −10 to −20 diopters. Pupillary membranes can be seen in the majority.

B. *The Transitional Fundus.*—From one to six weeks after birth there begins a rapid clearing of the vitreous, revealing a number of blood vessels of small caliber emerging from the disc. (See Plates I to III.) This stage of development is readily distinguishable from



A.

B.

Plate I.—Normal fundi oculi.

A, Immature fundus. The optic disc and blood vessels are barely discernible through the severe vitreous clouding. Diopters of focus −20. These fundi remained unchanged, except for fluctuating diopters of focus (−5 to −20), for three weeks.

B, Transitional fundus. The blood vessels are more numerous and larger but still distributed vertically. Vitreous clouding is less. The optic disc is well marginated. Several days prior to this picture the transition was more evident. −8 diopters.

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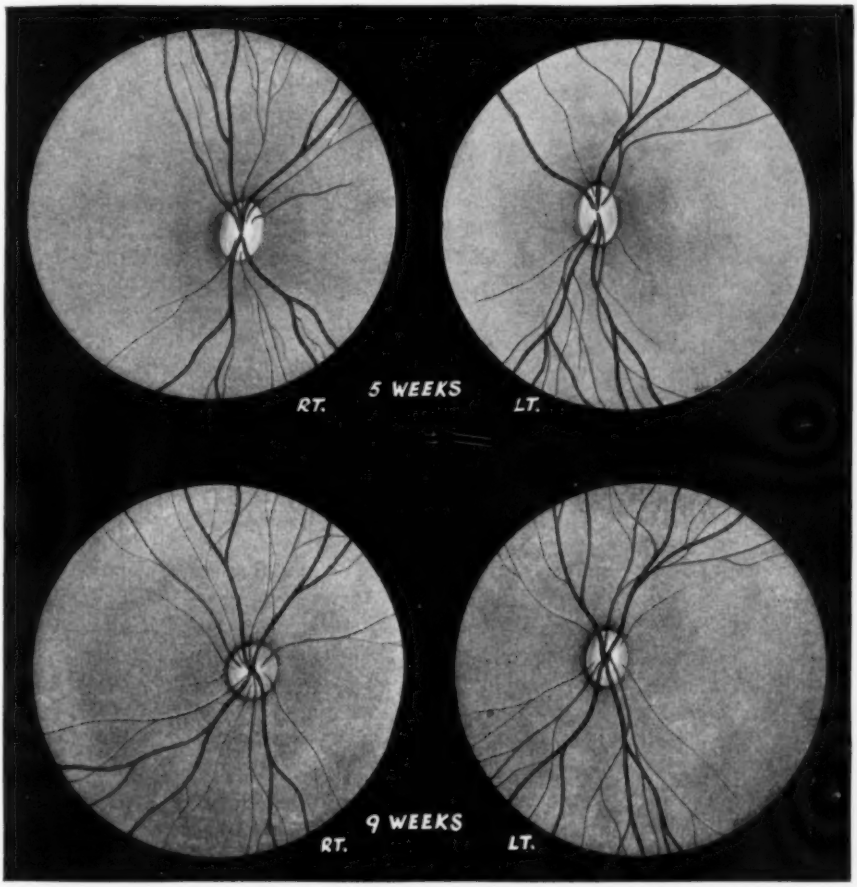


C.

D.

Plate I.—Cont'd.

C, Mature fundus. The optic disc is more rounded, with pigment deposited around the borders and in the retinas. The vitreous is clear with the disc and blood vessels sharply outlined. The blood vessels have an increased number of branches with a greater blood supply to the temporal and nasal areas. −6 diopters.

D, Normal fundus (as seen in the full-term infant). There has been no essential change over the ensuing four weeks, except further rounding of the optic disc and more extensive blood vessel branching. −3 diopters.

the immature and the mature stages. The disc changes shape, increasing in nasotemporal diameter, becoming more nearly spherical. It is now possible to identify arteries and veins separately. The nasal and temporal areas are lacking in visible blood supply and are often pale in color. The retinal reflex may be quite red but more often is pale, fading into a grayish periphery. Blood vessels seen against a slate gray periphery may elevate one to eight diopters, the phenomenon referred to by various authors as a "pseudodetachment." Pseudodetachment can be distinguished from a true retinal detachment in the following manner: it appears during the transitional or mature stage, is unaccompanied by other evidences of RLF, and has a characteristic slate gray color. True detachment occurs with other evidences of RLF and is characterized by a light yellow or greenish-yellow color. White streaks which may represent myelin sheaths often radiate out from the poorly marginated disc. Hyaloid remnants and pupillary membranes are almost universally seen. The transitional stage lasts usually one to two weeks, sometimes longer, and progresses on to the mature normal fundus comparable to that seen in full-term infants.

C. *The Mature Fundus.*—The mature fundus resembles the normal fundus of the full-term infant. It has greater clarity of the vitreous and an adult pattern of blood vessel distribution. The superior and inferior nasal and temporal branches of the retinal arteries and veins are distinguishable with end branches circling toward the macula and nasal areas. (See Plates I to III.) These vessels are moderate in size with normal highlights and can usually be seen in sharp focus at –2 to –10 diopters. The spherical disc is sharply outlined. Pigment begins to become visible about the disc margins simultaneously with its appearance in the skin of the Negro and heavily pigmented white races. The hyaloid remnants and pupillary membrane are quite small or completely absorbed. At the extreme periphery there is usually a fading of the pink retinal color to a light yellow. Pseudodetachments tend to disappear at this stage. Further evidence of maturation, such as differentiation of the macula, increase in size of the globe, increase in retinal pigmentation, further clearing of the vitreous, etc., have been fully described elsewhere.[1] (See Plates I to IV.) It is after this point in development, i.e., the mature stage, that a most significant change may take place. The eye may remain normal in appearance or go on to develop the early changes of retrolental fibroplasia.

RETROLENTAL FIBROPLASIA

As previously stated, when the mature stage is reached, the eye may remain normal or go on to develop the hypervascular early changes of retrolental fibroplasia (see Diagram I). All immature eyes go through the same maturation process before the appearance of the hypervascular stage. In those which become hypervascular, the vitreous, which has once been clear, again becomes cloudy, the disc margins become blurred, and the retina appears edematous. The veins become dilated to more than twice their normal size and the arteries show twisting and coiling. Not infrequently, tortuosity of the arteries precedes the rest of the picture and may appear before complete maturation (see Plate II). There

A.

B.

Plate II.—Retrolental fibroplasia, acute stage 3, with spontaneous recovery.

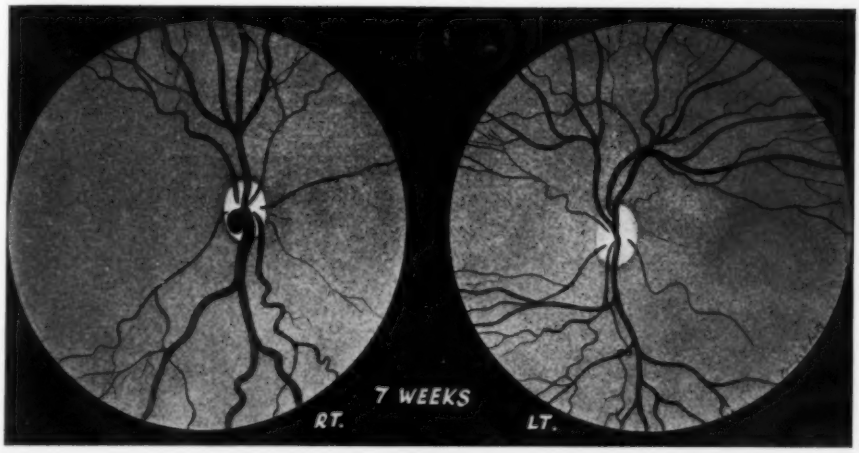
A, Immature fundus. The blood vessels are drawn with an exaggerated clarity. Vitreous clouding was extreme. −15 diopters.

B, Acute RLF, Stage 1. The eyes were examined three times in the interim between the first and this second picture. The features of the immature eye remained unchanged. This baby developed tortuous arteries and dilated veins with one retinal hemorrhage before complete transition occurred. This onset of RLF before complete maturation is unusual. −20 diopters.

C, Acute RLF, Stage 2. Enormous dilatation of the veins with marked tortuosity of the arteries and increased number of blood vessels. −20 diopters.

D, Acute RLF, Stage 3. The right eye contains a retinal detachment with a segment of a dilated blood vessel at the margin of the detachment. This is probably an aberrant vascular channel. −20 diopters.

E, Spontaneous regression. There remains only slight dilatation and tortuosity. Note the beginning deviation of the vessels temporally in the left eye. −6 diopters. At 6 months of age these fundi had the typical disc deformity of cicatricial RLF II. The blood vessels were pulled to the temporal side of each disc, *no* scar tissue was visible, and the macular areas were intact. Vision is apparently good.



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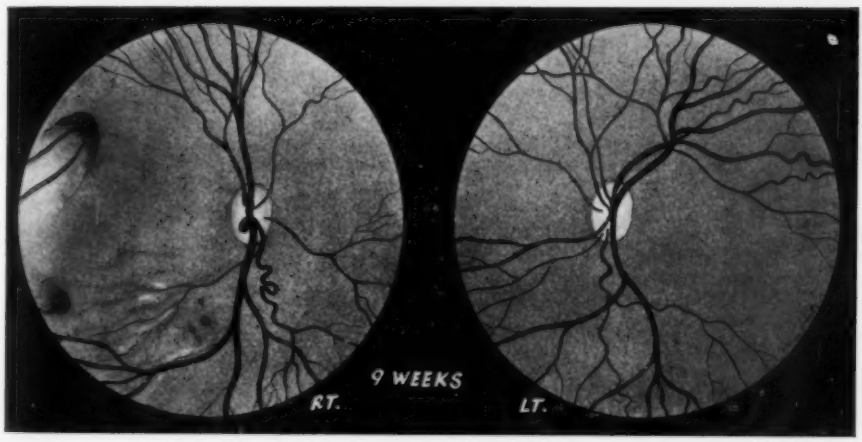

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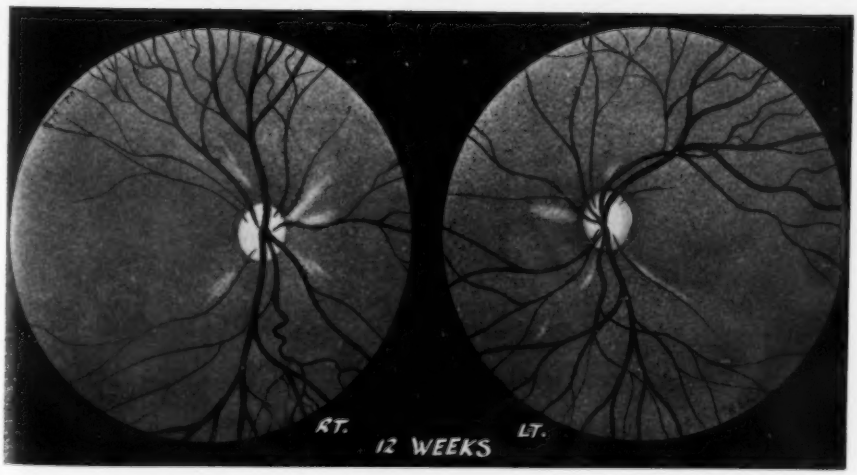

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Plate II.—Cont'd. *(For legend see opposite page.)*

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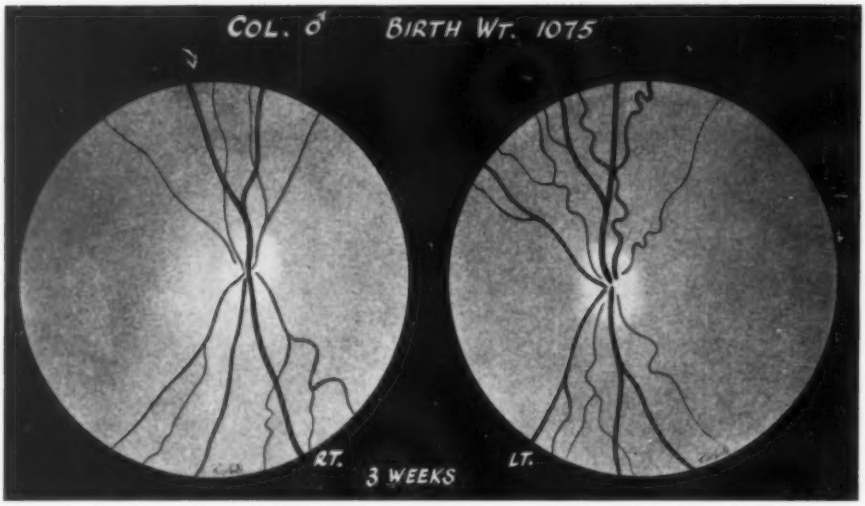

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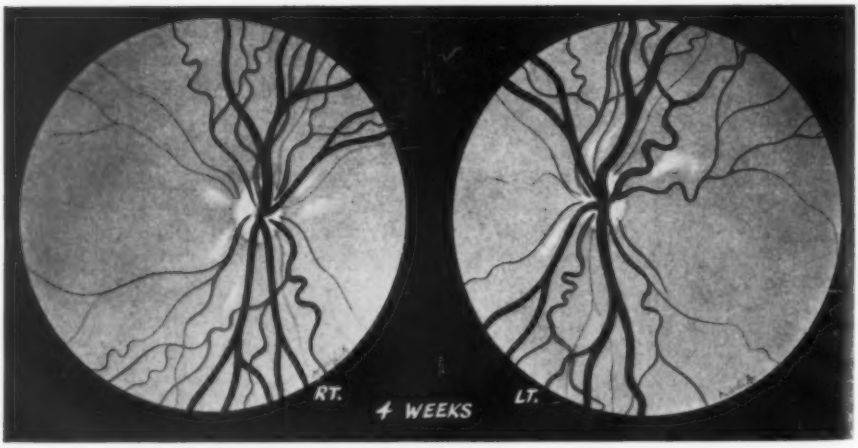
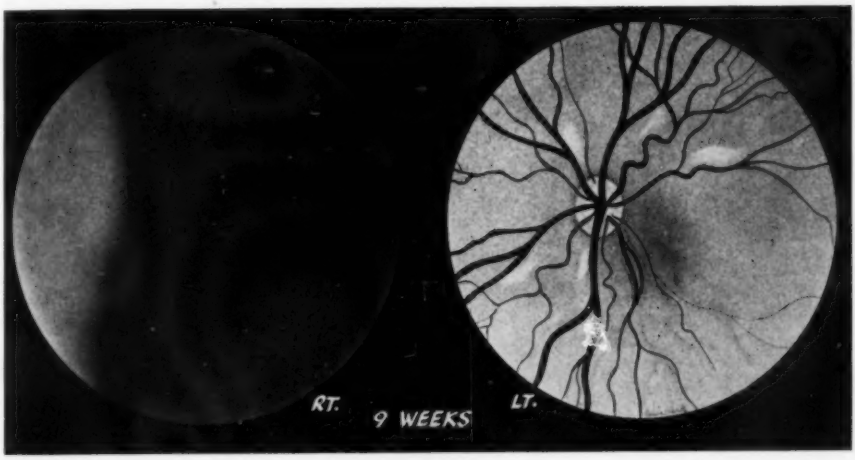


Plate III. Retrolental fibroplasia with vitreous hemorrhage.

A, Acute RLF, Stage 1. An immature eye was present at birth which became mature two days before this picture was drawn. Note the dilated and tortuous blood vessels. Vitreous clouding was present. −20 diopters.

B, Acute RLF, Stage 2. Blood vessels are enormously dilated and tortuous. −20 diopters.



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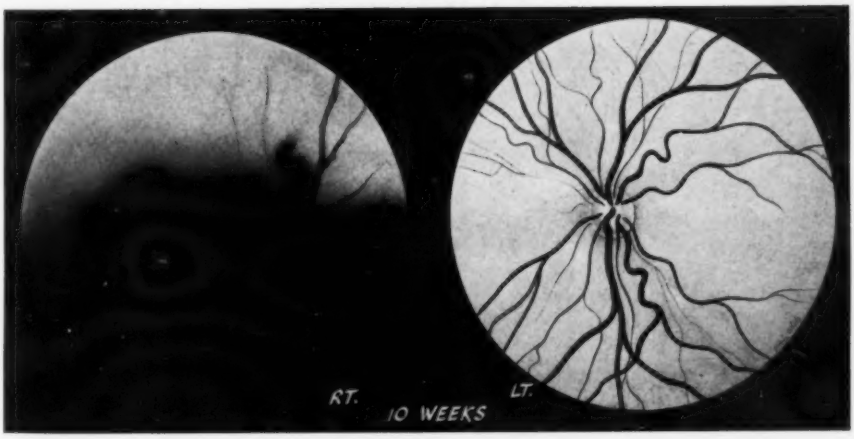


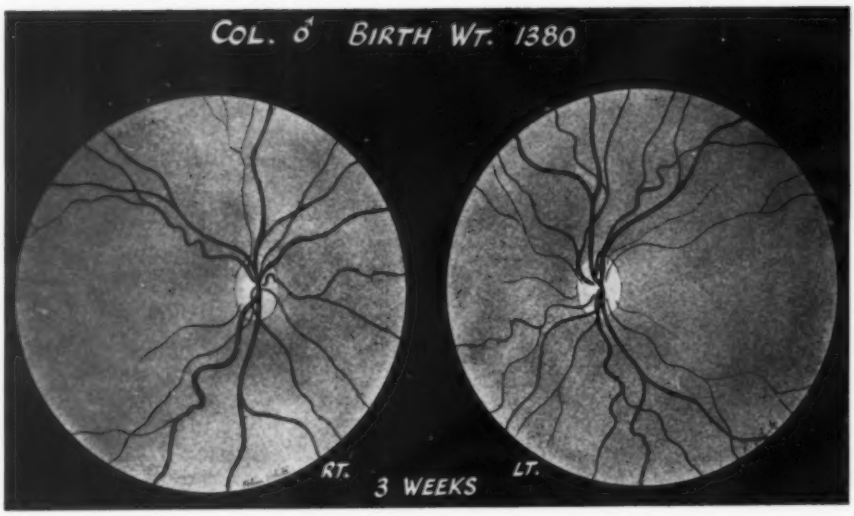
D.

Plate III.—Cont'd.

C, Acute RLF, Stage 3. The lesion in the left eye has subsided somewhat but vitreous hemorrhage occurred in the right eye. −8 diopters (left).

D, Acute RLF, Stage 3. Vitreous hemorrhage is beginning to organize and a detachment of the retina can be seen nasally. The left eye still has dilated and tortuous blood vessels. Four weeks after this picture the left retina became detached. The child ultimately had a cicatricial RLF Stage 5 (Rt.) and Stage 3 (Lt.) Vision is severely impaired.

A.



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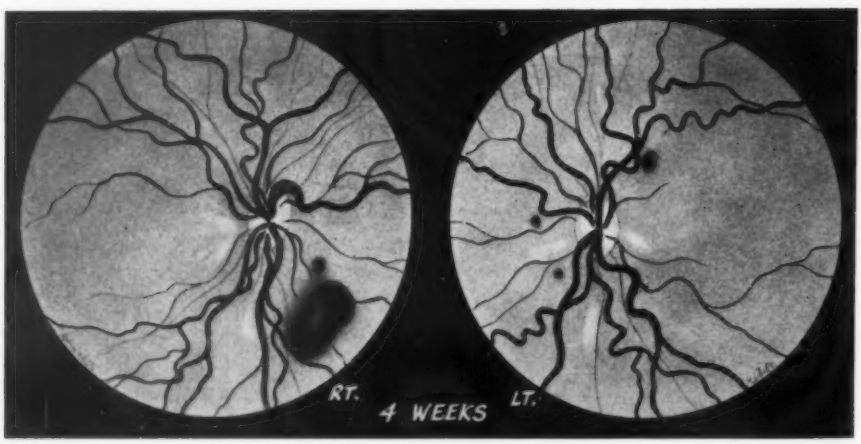


Plate IV.—Retrolental fibroplasia with blindness.

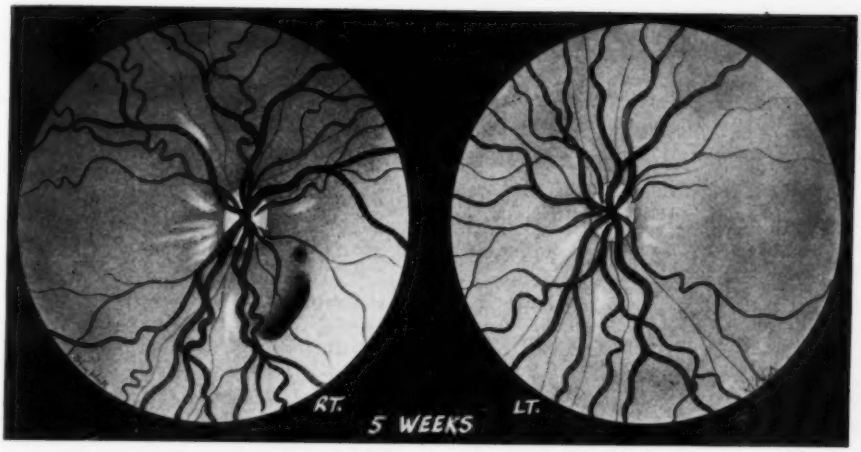
A, Acute RLF, Stage 1. The eyes were not examined previously. Note the dilated and tortuous blood vessels. −5 diopters.

B, Acute RLF, Stage 2. Enormous blood vessels with edema of the retina and retinal hemorrhages. −5 diopters.

C, Acute RLF, Stage 3. Retinal detachment bilaterally, increased vitreous clouding, and new vessel formation. −6 diopters.

D, Acute RLF, Stage 4. The lesion on the left has subsided somewhat, whereas three-quarters of the right retina has become detached.

E, Acute RLF, Stage 5. The right eye, seen with a plus 20 lens, shows a completely detached retina lying just behind the lens. The left eye, seen with a plus 6 lens, shows hemispherical retinal detachment. This child ultimately became totally blind, cicatricial RLF, Stage 5.



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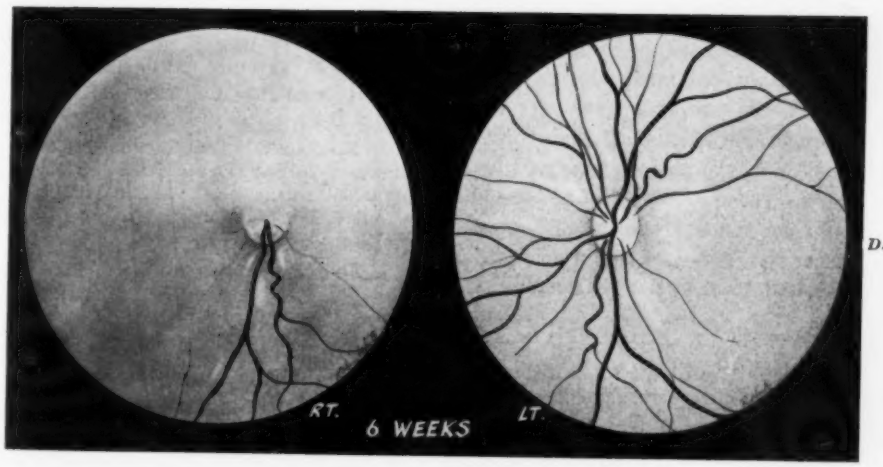

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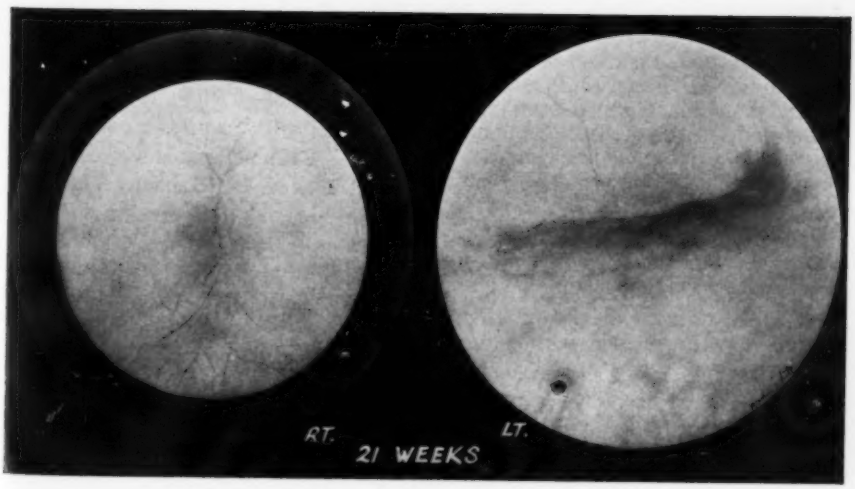


E.

Plate IV.—Cont'd. *(For legend see opposite page.)*

is an increased red retinal reflex and the number of visible capillaries increase at the disc margin as well as in the periphery. Small retinal hemorrhages may be seen, usually in the sector most engorged with vascular tissue and edema. The hypervascular eye contains more blood and fluid than the normal eye and often becomes quite tense on palpation. Iritis may appear and the anterior chamber may vary in depth.

Again a divergence in clinical pattern may become evident. After the early lesions have developed, they may remain without much change for several weeks and then gradually disappear, or the lesions may show progression on to the severe stages of the disease. The lesions have been classified into five stages according to degrees of severity. This is a modification of the original classification of Reese.[2]

Acute Stages:

1. Dilatation and tortuosity of retinal vessels. Retinal hemorrhages may or may not be present. Early neovascularization in the extreme periphery of the visible fundus may be present. Minor vitreous clouding. Mild disc and retinal edema.

2. Stage 1 plus marked neovascularization (spiders) and some peripheral retinal clouding. Retinal hemorrhages are usually present. Vitreous clouding is usually severe. Spontaneous regression usually occurs.

3. Stage 2 plus retinal detachment in the periphery of the fundus. Vitreous or severe retinal hemorrhage. Retinal folds may be present.

4. Hemispherical or circumferential retinal detachment. Elevation of the retina over a large area but still with some retina in position.

5. Complete retinal detachment.

Cicatricial Stages:

1. Small mass of opaque tissue in the periphery of the fundus without visible retinal detachment. The fundus may have a pale appearance. The blood vessels may be attenuated. The mass is usually temporal.

2. Larger mass of opaque tissue in the periphery of the fundus with some localized retinal detachment. The disc is distorted by traction toward the side of the tissue which is usually temporal. Persistent mild myopia. Cases ending in Stages 1 or 2 have useful vision with maximum correction.*

3. Larger mass of opaque tissue in the periphery incorporating a retinal fold which extends to the disc. Persistent high myopia. Visual acuity varies from 5/200 to 20/50, corrected.*

4. Retrolental tissue covering part of the pupillary area. Small area of attached retina may still be visible or a red reflex over only a sector of the fundus may be seen.

5. Retrolental tissue covering the entire pupillary area. No fundus reflex present.

During the years 1950 to 1953 at Jefferson Davis Hospital, 246 babies under 2,500 grams were examined to determine the incidence of occurrence of acute RLF in this nursery (see Table V). Of the 246 infants, 182 were Negro with 20 per cent incidence of RLF, whereas in 64 white (36 per cent) developed RLF. This difference is statistically significant (see Tables VI and VII). There is likewise a high incidence of RLF among the white babies in the private nurseries of Houston. Of 50 babies examined, 26 had RLF and 24 were normal (see Table VIII).

There was a significantly increased incidence of RLF in males as compared

*According to Dr. Reese. The infants in this study are as yet too young for subjective visual evaluation.

with females. At Jefferson Davis Hospital, 30 per cent of males and 19 per cent of females had RLF (see Tables IX and X). In the private babies, 59 per cent of the males and 43 per cent of the females had RLF.

In 1950 and 1951 at Jefferson Davis Hospital, 76 babies over 1,700 grams

TABLE V. INCIDENCE OF PREMATURE INFANTS WITH NORMAL FUNDI AND THOSE WITH RLF ACCORDING TO BIRTH WEIGHT GROUPS, 1950-1953, JEFFERSON DAVIS HOSPITAL. THE PER CENT INCIDENCE OF OCCURENCE OF RLF UNDER 1,700 GRAMS BIRTH WEIGHT FOR 1950, 1951, AND 1952 IS 34, 22, AND 41, RESPECTIVELY

BIRTH WEIGHT GRAMS	1950				1951				1952			
	OK	RLF	TOTAL	% WITH RLF	OK	RLF	TOTAL	% WITH RLF	OK	RLF	TOTAL	% WITH RLF
2,001-2,500	14	2	16	12	15	0	15	0				
1,701-2,000	16	3	19	16	25	1	26	4				
1,501-1,700	7	2	9	22	30	2	32	6	19	10	29	36
1,250-1,500	14	4	18	22	17	7	24	29	13	5	18	28
1,001-1,250	3	3	6	50	8	7	15	47	2	8	10	80
<1,000	1	4	5	80	2	0	2	0	0	2	2	100
Total	55	18	73	25	97	17	114	15	34	25	59	42

TABLE VI. NEGRO BABIES. INCIDENCE OF NORMAL AND RLF FUNDI IN 182 NEGRO PREMATURE INFANTS, JEFFERSON DAVIS HOSPITAL, 1950 TO 1953

BIRTH WEIGHT GRAMS	NORMAL	RLF	TOTAL	% RLF
2,001-2,500	23	0	23	0
1,701-2,000	33	3	36	8
1,501-1,700	42	6	48	13
1,251-1,500	32	11	43	26
1,001-1,250	12	12	24	50
<1,000	3	5	8	63
Total	145	37	182	20

TABLE VII. WHITE BABIES. INCIDENCE OF NORMAL AND RLF FUNDI IN 64 WHITE PREMATURE INFANTS, JEFFERSON DAVIS HOSPITAL, 1950 TO 1953

BIRTH WEIGHT GRAMS	NORMAL	RLF	TOTAL	% RLF
2,001-2,500	6	2	8	25
1,701-2,000	8	1	9	11
1,501-1,700	14	8	22	36
1,251-1,500	12	5	17	30
1,001-1,250	1	6	7	86
<1,000	0	1	1	100
Total	41	23	64	36

Statistical significance: RLF occurred in a significantly higher percentage of white infants than in Negro.

The standard error of difference is 6.5 and the percentage difference is 16. This difference is more than twice the standard error.

TABLE VIII. INCIDENCE OF NORMAL AND RLF FUNDI IN 50 PREMATURE INFANTS BORN IN PRIVATE HOSPITALS, HOUSTON, 1952

BIRTH WEIGHT GRAMS	NORMAL	RLF	TOTAL	% RLF
1,701-2,000	5	2	7	29
1,501-1,700	3	3	6	50
1,251-1,500	9	8	17	47
1,001-1,250	2	9	11	82
<1,000	5	4	9	44
Total	24	26	50	52

were examined and 6 found to have developed mild RLF with no residual lesions. Because of the low incidence of the disease in the higher weight groups, only infants with birth weights under 1,700 grams have been examined since 1951.

Among the private babies, 12 of the 26 with RLF remained benign (see Table XI). In both groups the subsequent picture was similar; the vitreous clouding decreased, hypervascularity diminished, and retinal and disc edema became less evident. The eyes

TABLE IX. MALE. INCIDENCE OF NORMAL AND RLF FUNDI IN 120 MALE PREMATURE INFANTS, JEFFERSON DAVIS HOSPITAL, 1950 TO 1953

BIRTH WEIGHT GRAMS	NORMAL	RLF	TOTAL	% RLF
2,001-2,500	15	0	15	0
1,701-2,000	19	3	22	14
1,501-1,700	27	11	38	29
1,251-1,500	18	11	29	38
1,001-1,250	4	10	14	71
<1,000	1	1	2	50
Total	84	36	120	30

Statistical significance: RLF occurred in a significantly higher percentage of male than female infants. The standard error of difference is 5.4 and the percentage difference is 11. This percentage difference is twice the standard error.

TABLE X. FEMALE. INCIDENCE OF NORMAL AND RLF FUNDI IN 126 FEMALE PREMATURE INFANTS, JEFFERSON DAVIS HOSPITAL, 1950 TO 1953

BIRTH WEIGHT GRAMS	NORMAL	RLF	TOTAL	% RLF
2,001-2,500	14	2	16	13
1,701-2,000	22	1	23	4
1,501-1,700	29	3	32	9
1,251-1,500	26	5	31	16
1,001-1,250	9	8	17	47
<1,000	2	5	7	71
Total	102	24	126	19

TABLE XI. INCIDENCE OF RLF IN PREMATURE INFANTS, DIVIDED INTO FINAL ACUTE STAGES, JEFFERSON DAVIS HOSPITAL AND PRIVATE HOSPITALS, HOUSTON, 1950 TO 1953

	JEFFERSON DAVIS HOSPITAL				PRIVATE HOSPITALS
ACUTE RLF	1950	1951	1952	TOTAL	1952
1	10	7	11	28	9
2	3	4	1	8	3
3	2	3	12	17	8
4	1	0	1	2	2
5	2	3	0	5	4
Total	18	17	25	60	26

A. *Mild Retrolental Fibroplasia.*— The onset of hypervascularity or acute RLF, Stage 1, occurred in this nursery two to seventy-six days, or an average of fifteen days, after the eyes became mature. (See Table XV.)

Of the 60 Jefferson Davis Hospital babies with RLF, 36 remained benign and did not progress beyond Stage 2. became normal three to 104 days, or an average of twenty-five days, after the appearance of RLF, Stage 1. (See Table XV.) Only one infant of these has at present any residual of his disease (see Tables XII and XIII). This child, now 2½ years old, had a severe and persistent RLF, Stage 2, for which he was treated with ACTH for three

weeks. He now has a persistent high myopia (–20 diopters).

Huggert[3] of Stockholm has observed hypervascularity and edema which he suggests might be normal stages of development. He has observed no severe RLF.

XIII.) This infant, whose fundi appear in Plate II, had a mild retinal detachment which disappeared spontaneously in a few days with residual temporal scar and disc deformity. Although racial and sex differences are important in the incidence of the disease, they do not appear significant in the severity of the disease. However, it is significant that the more immature the infant, the greater the severity of the disease (see Diagrams 2, 3, and 4).

TABLE XII. PRESENT VISUAL STATUS OF 246 PREMATURE INFANTS, JEFFERSON DAVIS HOSPITAL, 1950 TO 1953

		TOTAL NO. OF BABIES	NORMAL	RESIDUALS OF RLF					NO FOLLOW-UP	DIED
				USEFUL VISION		IMP. VISION	BLIND			
				1	2	3	4	5		
1950	Normal	55	40						15	
	Acute RLF	18	12		1	1	2	2		
	Total	73	52		1	1	2	2	15	
1951	Normal	97	73						21	3
	Acute RLF	17	9			2		3	1	2
	Total	114	82			2		3	22	5
1952	Normal	34	15						19	
	Acute RLF	25	10						8	2
				2	2	1				
	Total	59	25	2	2	1			27	2

TABLE XIII. PRESENT VISUAL STATUS OF 35 PREMATURE INFANTS WITH RETROLENTAL FIBROPLASIA, JEFFERSON DAVIS HOSPITAL, 1950 TO 1951. CICATRICIAL STATUS IS GIVEN FOR THE BETTER EYE ONLY

ACUTE RLF	TOTAL NUMBER OF BABIES	NORMAL	RESIDUALS OF RLF					NO FOLLOW-UP	DIED
			USEFUL VISION		IMP. VISION	BLIND			
			1	2	3	4	5		
1	17	17							
2	7	4			1*			1	1
3	5			1†	2	1			1
4	1					1			
5	5						5		
Total	35	21		1	3	2	5	1	2

*Residual high myopia.
†See Plate II for drawings of this patient.

B. *Severe Retrolental Fibroplasia.*—Thirty-eight severe cases of acute RLF, Stages 3, 4, and 5, have been observed, 24 in Jefferson Davis Hospital patients, and in 14 private patients in local hospitals. (See Table XI.) In 1950 and 1951, all of the severe lesions at Jefferson Davis Hospital progressed to severely impaired vision or total visual loss with one exception. (See Table

RETINAL VASCULAR DYNAMICS

It appears from the foregoing observations that premature infants,

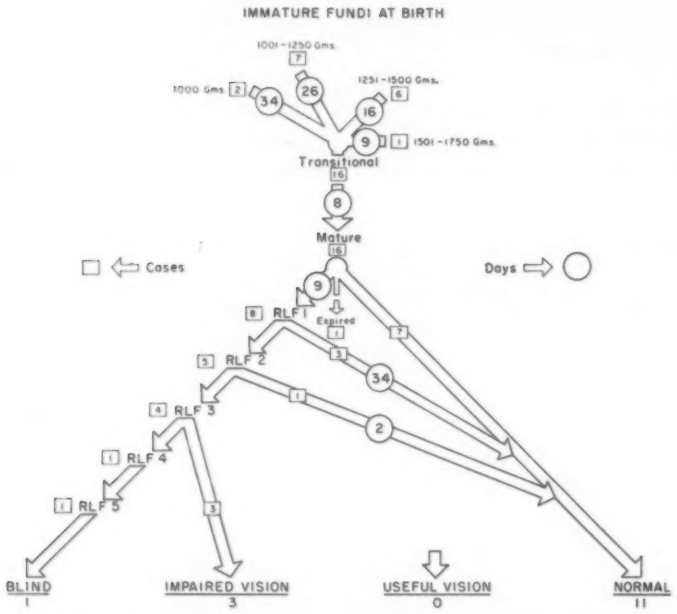


Diagram 2.—Immature fundi development. Graphic presentation of incidence of RLF in infants born with immature fundi. Only those infants who were adequately examined from birth to 6 months are included, Jefferson Davis Hospital, 1950 to 1951. Fifty per cent of these infants developed mild RLF and 25 per cent developed severe RLF. This is statistically significant. The standard error of difference between those born with mature fundi is 12.5. The percentage difference of 46 is almost four times the standard error of difference.

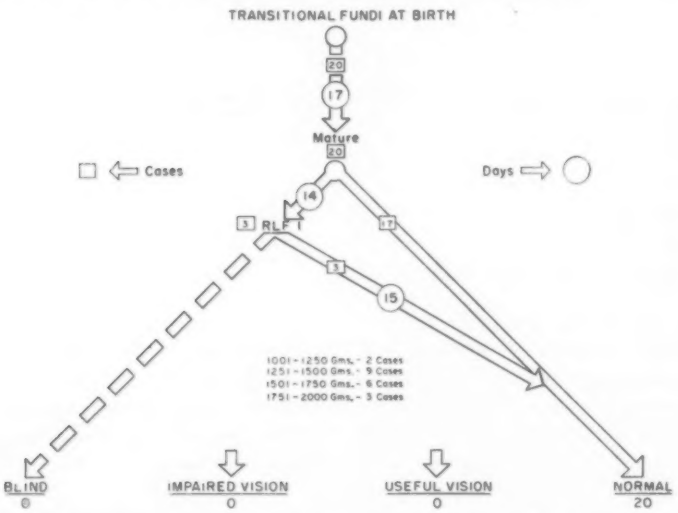


Diagram 3.—Transitional fundi development. Graphic presentation of incidence of RLF in infants born with transitional fundi. Fifteen per cent of these infants developed mild RLF with *no* severe forms of the disease. Those developing RLF weighed 1,300, 1,335, and 1,560 grams at birth.

whether destined to develop or escape RLF, progress through a process of normal maturation of the fundus. The first appearance of RLF occurs after maturation. The question then arises as to the ocular dynamics involved in the development of dilated tortuous vessels, neovascularization, vitreous clouding, and retinal edema. Since these changes represent the onset of the disease, the further progress of RLF might be checked by alteration of the early manifestations.

In early RLF, if the initial lesions were due to a relaxed tone of blood vessel walls, contraction of the smooth muscle might be brought about by autonomic drugs. An attempt was made to change the tonus of the retinal blood vessels. Six infants with mild RLF were given Adrenalin, ephedrine, and/or pilocarpine until physiologic effects were obtained and their fundi examined. No contraction of the blood vessels was noted, none of the lesions

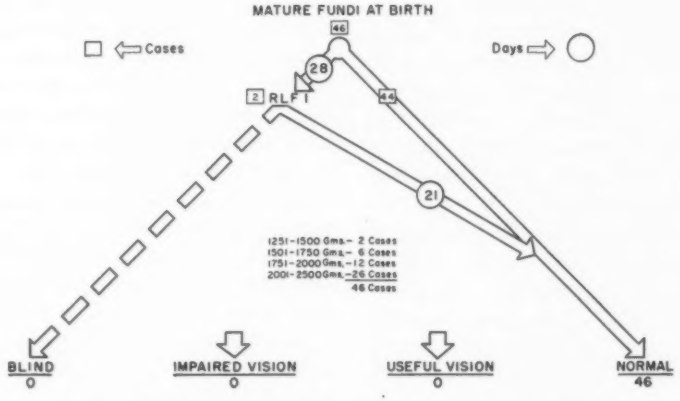


Diagram 4.—Mature fundi development. Graphic presentation of incidence of RLF in infants born with mature fundi or fundi resembling those of the full-term infant. Only 4 per cent developed mild RLF with *no* severe disease. These infants weighed 1,370 and 1,650 grams at birth.

Friedenwald,[4] in his excellent discussion of "Retinal Vascular Dynamics," suggested three possible causes of dilated and tortuous retinal vessels and of excessive vascular channels.

1. Relaxed tone of vessel walls.
2. Increased arterial tension or flow.
3. Decreased peripheral resistance.

Dr. Friedenwald's suggestions of principles involved were followed in an attempt to apply them clinically to the situation existing in the eye of the premature infant with retrolental fibroplasia.

abated abruptly, and two of the six infants progressed on to severe RLF.

Increased retinal arterial tension or flow was next considered as a factor in the production of first stage RLF. Two possibilities were considered: primary ophthalmic hypertension and systolic hypertension accompanied by an increase in ophthalmic blood pressure. The second possibility was capable of clinical evaluation here. Systolic blood pressures were measured in the brachial arteries by a variation of

the flush method* in 66 infants at weekly intervals from birth to approximately 3 months of age. Of the 66, 27 weighed less than 1,500 grams and 39 weighed 1,500 to 2,000 grams at birth. In the infants weighing less than 1,500 grams, RLF developed in 11, 4 in severe form. Infants who developed RLF showed no demonstrable increase in blood pressure over those who escaped the disease.

Decreased peripheral resistance, implying a faster flow of blood through the vascular bed, was mentioned as a third possibility by Friedenwald as a cause of dilated and tortuous retinal blood vessels. Here again two possibilities were considered: active local congestion secondary to infection, and an increase in number of vessels secondary to unknown factors. Infection as an etiological factor has not been investigated here, although it has been considered by several authors.[5] However, it does not seem likely that any infectious agent could cause a disease which adheres so closely to a growth pattern and its etiological significance therefore seems unlikely. It is true that in RLF there is an increase in the number of blood vessels.

It has not been demonstrated that the stillborn premature fetus of any gestational age has excessive vascular tissue in the retina and vitreous. In the cases reported here no hypervascularity has been noted at birth in any premature infant regardless of gestational age. The eye may pass through several stages before reaching the mature or full-term eye, but it is only after reaching the latter stage that hypervascularization develops. In 50 per cent of the babies born with fundi classified as immature, in 15 per cent born with fundi classified as transitional, and in only 4 per cent born with fundi classified as mature, did excessive vascular tissue develop (see Diagrams 2, 3, and 4). It is significant that those infants born with immature fundi have a greater tendency to produce excessive vascular tissue and to manifest the disease RLF.

Many factors suggest themselves as possible causes of this phenomenon. One at present in the forefront is oxygen. It has been shown that the fetus in utero lives in an atmosphere of lowered oxygen tension. Consequent to premature birth and exposure of the infant to 40 to 60 per cent oxygen atmospheres in incubators, maturation of the eye is carried on in the presence of a higher oxygen tension than would be present in utero. Gyllensten[6] has recently demonstrated that an atmosphere excessive in oxygen does have a deleterious effect upon the eyes of newborn mice. He has produced changes in the eyes of newborn mice similar to those of severe RLF seen in human subjects. Dickins[7] has demonstrated in very careful experiments that excessive oxygen may irrevocably alter metabolism of rat brain slices as well as the metabolism of other organs and tissues. His experience suggests that the high incidence of brain damage as well as RLF reported in the premature infant by Krause[8] may possibly be related to this excessive oxygen administration.

A second mechanism, that of rapid oxygen withdrawal,[9] may also be of importance. Duguet[10] and others before him have demonstrated this phenomenon in adults. They used motion pictures of the retinas to demonstrate a 10 to 20 per cent increase in diam-

*Method and results to be published elsewhere.

eter of retinal vessels for every 16,000 to 19,000 feet of elevation above sea level, an effect immediately relieved by the administration of oxygen. Crosse[11] and Holmdahl[12] have not given their incidence of early RLF developing under low oxygen administration. These would be most valuable observations.

Other factors besides oxygen excess or deficiency may operate in the production of neovascularization in the premature eye. The significant difference in incidence of the disease in different races and sexes may be related to differences in maturity and survival, but the sex difference in incidence also may be due to hormonal influences on the developing eye structures. The added stress of the premature infant's worldly existence must certainly make increased demands upon immature hormonal mechanisms.

In addition to the hypervascularity and dilated tortuous retinal vessels seen in RLF, there is an excessive accumulation of fluid as manifested by edema of the retina and optic disc, vitreous clouding, edema of the cornea and iris, retinal folding, and accumulation of transudate. The excess fluid may be secondary to an active local congestion, may be an expression of the generalized edema shown by some of these infants,[13] or may be secondary to factors as yet unknown.

Excessive intraocular fluid may increase intraocular tension. An attempt was made to demonstrate this increased intraocular tension both with a Harrington-Parsons tonometer* and by digital palpation. Technical difficulties prohibited definitive conclusions with the tonometer. However, infants with RLF tend to show evidences of increased intraocular pressure, clinically observed as increased prominence and firmness of the eyeball.

Related to, and supporting, the question of increased intraocular tension may be the wide variation noted in focal distances of the retinal vessels at the disc margin. In the nursery at Jefferson Davis Hospital, different observers, measuring the focal distance on the same eye at the same time, with the ophthalmoscope, varied within 3 to 5 diopters in the low minus range and 5 to 10 diopters in the high minus range. But never has one observer obtained a sharp focus with low minus and the other with a high minus lens. Of 72 cases analyzed by plotting the observed focal distances semilogarithmically and measuring the area beneath the curve during the first ten weeks of life, it was observed that the smaller the infant the higher the myopia. In other words, an observed high myopia of –10 to –20 diopters in the developing premature infants' eyes indicates immaturity and greater susceptibility to severe RLF (see Table XIV and Graph 2).

The mechanism underlying the myopia is obscure but is likely due to (1) increased and fluctuating depth of the vitreous chamber, (2) changes in size of the lens, or (3) changing depth of the anterior chamber with the resulting changes in corneal curvature. These observations may lend support to the supposition that in infants with retrolental fibroplasia there is an increased and fluctuating amount of intraocular fluid.

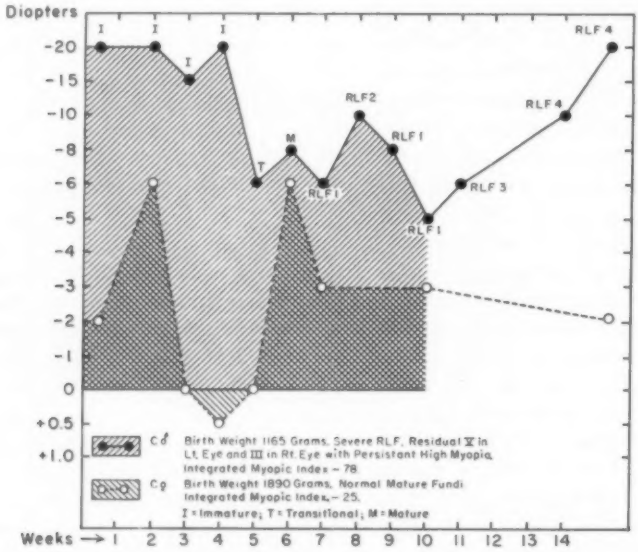
The myopia observed early in the disease may remain as a residual lesion after the disease has become inactive. Whether this persistent myopia belongs in the group of progressive con-

*Courtesy of Dr. Harrington.

genital myopias or will be transitory in nature remains to be answered by more extended observations.

SUMMARY

The development of the eyes of 320 premature infants, most of whom have weighed less than 1,700 grams at birth, has been followed over a three-year period. Very small premature babies are born with an immature fundus which passes through a transitional stage before reaching the mature fundus similar to that of the full-term



Graph 2.—Integrated myopic index. The diopter recorded in each instance is that lens required to bring into sharp focus the retinal vessels at the disc margin. These diopters are plotted semilogarithmically from birth to 10 weeks of age and the area beneath the curve measured with a planimeter and expressed as "integrated myopic index."

TABLE XIV. COMPARISON OF THE MEAN INTEGRATED MYOPIC INDICES IN PREMATURE INFANTS OF VARIOUS BIRTH WEIGHTS*

	BIRTH WEIGHT IN GRAMS											
	< 1,500				1,500-1,700				> 1,700			
FUNDI	NO.	RANGE	MEAN	STANDARD ERROR	NO.	RANGE	MEAN	STANDARD ERROR	NO.	RANGE	MEAN	STANDARD ERROR
Normal	15	29-84	62	3.3	11	–12-74	43	6.6	18	15-75	38	3.3
Mild RLF[1, 2]	10	31-91	56	6.5	5	37-78	60	5.4	2	40-45	43	5
Severe RLF[3, 4, 5]	11	66-96	79	3.9								

Statistical analysis:

(1) The standard error of difference between those infants <1,500 grams birth weight who developed severe RLF and infants >1,700 grams with normal fundi is 5.1. The difference between their area of myopia is 41, or eight times greater than the standard error of difference and is therefore highly significant.

(2) The standard error of difference between infants with birth weights less than 1,500 grams compared with infants of birth weight more than 1,700 grams is 4.6. The difference in myopia between these two is 24, or five times greater than the standard error of difference.

(3) The standard error of difference between the infants with normal and RLF fundi less than 1,500 grams birth weight is 5.1. The observed difference in myopia is 17, or three times the standard error of difference and is therefore significant.

*See Graph 2 for method of obtaining the integrated myopic index. There is a highly significant increase in the myopic index in smaller infants compared with larger infants and in infants with severe RLF as compared with infants whose eyes remained normal.

TABLE XV. DEVELOPMENT OF THE EYE*

BIRTH WT. GRAMS	IMMATURE						MATURING						MATURE					
	AGE			WT.			AGE			WT.			AGE			WT.		
	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.
More than 2,000													31	(All Mature—No RLF)				
1,759 to 2,000	—	(None)	—				3	2 to 14	7	3	1,760 to 2,250	1,960	15	2 to 21	8	15	1,770 to 2,320	1,970
1,501 to 1,750	8	1 to 7	3	8	1,500 to 1,730	1,600	18	1 to 22	9	17	1,380 to 1,750	1,600	44	2 to 36	13	43	1,500 to 2,080	1,670
1,251 to 1,500	21	0 to 16	6	21	1,280 to 1,550	1,420	32	1 to 43	15	31	1,300 to 2,300	1,490	46	12 to 50	20	45	1,300 to 2,500	1,580
1,001 to 1,250	26	2 to 28	9	25	1,000 to 1,400	1,140	28	8 to 56	23	27	1,021 to 1,980	1,260	27	11 to 94	34	26	1,050 to 2,000	1,410
Less than 1,000	11	4 to 56	21	11	875 to 1,200	980	10	21 to 63	43	10	1,060 to 1,600	1,310	10	28 to 70	51	10	1,220 to 1,790	1,440

(*Continued on next page.*)

TABLE XV—CONT'D

	RLF I						RLF II						RLF III					
	AGE			WT.			AGE			WT.			AGE			WT.		
	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.
More than 2,000								(All Mature—No RLF)										
1,759 to 2,000	2	19 to 43	31	2	2,200 to 2,500	2,300												
1,501 to 1,750	18	26 to 96	42	18	1,535 to 3,200	2,020	8	37 to 63	47	8	1,800 to 3,200	2,150	5	39 to 69	51	5	1,800 to 2,780	2,800
1,251 to 1,500	18	11 to 102	51	18	1,200 to 2,700	1,960	10	20 to 63	40	10	1,380 to 2,650	1,910	7	29 to 84	40	7	1,470 to 3,400	1,900
1 001 to 1,250	23	21 to 81	45	22	1,150 to 2,600	1,700	19	28 to 85	58	18	1,300 to 2,730	1,990	18	32 to 120	62	17	1,610 to 3,500	2,080
Less than 1,000	9	37 to 92	63	9	1,360 to 2,300	1,825	2	80 to 106	93	2	1,600 to 2,400	2,000	2	83 to 120	102	2	1,650 to 2,500	2,070

TABLE XV—CONT'D

	RLF IV						RESIDUAL SCARRING						RETURN TO NORMAL					
	AGE			WT.			AGE			WT.			AGE			WT.		
	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.	NO.	RANGE	AVER.
More than 2,000							(All Mature—No RLF)											
1,759 to 2,000													2	25 to 76	50	2	2,500 to 3,500	3,000
1,501 to 1,750	1	77 to 78	77	1	3,300 to 3,200	3,300	1	114 to 90	114	1	3,000 App.	3,000 App.	9	32 to 120	75	7	1,750 to 5,000	2,250
1,251 to 1,500	2	81 to 84	81	2	4,100 to 5,000	4,100	7	150 to 180	150	2	4,000 to 6,000	4,000	10	27 to 120	71	10	1,750 to 6,000	3,600
1,001 to 1,250	6	63 to 125	90	6	2,200 to 3,350	2,760	14	90 to 240	144	13	2,050 to 3,160 App. 5,000		9	49 to 125	85	9	1,500 to 5,000	2,530
Less than 1,000	None						2	120 to 180	150	2	2,800 to 3,200	3,000	6	49 to 138	91	5	1,680 to 2,800	2,200

*Analysis of the fundi of 245 premature infants in Jefferson Davis Hospital and in the private nurseries of Houston, Texas. They are divided into groups according to birth weight. The age (in days) and the weight (in grams) at which the infants' fundi attained different stages of maturation and development of RLF are given. The number of infants examined in each category, ranges, and averages are included.

infant. After maturation has been reached, the eye may remain normal or may progress on to show the early changes of retrolental fibroplasia. The early changes in turn may reverse spontaneously or may progress to the severe stages of the disease with varying degrees of visual impairment.

Of the 320 infants examined, 86 had retrolental fibroplasia, 38 of whom developed massive retinal edema with detached retinas and malignant hemorrhages. There was a statistically significant increased incidence of RLF in the white and male infants, which may possibly be related to a greater immaturity and poorer survival rate. It is also significant that the smallest infants and those with the most immature fundi at birth are the ones most likely to develop severe RLF with its resulting blindness. Evidence is presented to show that the small premature infant and those infants with severe RLF have a high and fluctuating myopia, which may remain as a residual lesion.

The parts played by (1) relaxed tone of blood vessel walls, (2) increased arterial tension, and (3) decreased peripheral resistance in the pathogenesis of the early stages of RLF were considered critically. It could not be demonstrated, within the limits of this study, that they were of significance. The role of excessive oxygen administration and rapid changes of oxygen environment in relation to hypervascularity were discussed. From the observations reported herein, the disease, retrolental fibroplasia appears to result from an as yet unknown factor or series of unknown factors affecting an immature eye which is passing through a period of critical differentiation and maturation.

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SALMONELLOSIS COMPLICATED BY PANCARDITIS

Report of a Case With Autopsy Findings

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CARDIAC involvement following Salmonella infection is rare. In reviewing this group of infections, exclusive of *Salmonella typhosa*, between 1904 and 1936, Wells[1] found reports on 320 autopsies. Survey of the English literature since 1947 has revealed only three additional cases of cardiac involvement with salmonellosis. An exhaustive search of the literature has failed to disclose any cases of either acute myocarditis or pancarditis due to this group of organisms. For this reason we are reporting a case of what is believed to be the first autopsied case of Salmonella pancarditis.

CASE REPORT

A 2-year-old male Negro child was admitted to Dooley Hospital of the Medical College of Virginia on Feb. 9, 1951, because of diarrhea and vomiting.

The child had been in good health until four days prior to admission when, according to his mother, he began to have "one stool right after another" which consisted of watery, yellowish material. This was accompanied by vomiting and anorexia. The previous night he had been seen in the Emergency Room with a temperature of 105° F. (rectal), and a diagnosis of "infected ear" was made. After the child was given an alcohol sponge bath and an injection of procaine penicillin, the parents were instructed to return with him to the Pediatric Clinic the following day. In the Clinic the following morning the patient was found to have a temperature of 100.6° F. (rectal) and the complaints were of the child's failure to talk and of an "ear infection." Examination at that time revealed some slight injection of the left tympanic membrane, a rapid heart rate without murmur, a palpable spleen 1 cm. below the left costal margin, and moderate dehydration. Laboratory studies at that time showed: hemoglobin 9.0 grams, red blood corpuscles 3,000,000, white blood cells 2,000 (rechecked) with 50 per cent polymorphonuclears and 50 per cent lymphocytes. No immediate sickling was seen. Flocculation test for syphilis was reported as negative at a later date. It was felt that the otitis media was subsiding and did not require further therapy. Multivitamin capsules and liver extract were given the parents along with instructions concerning proper diet, and the patient was to be seen again in one month unless he did not improve. That evening he was brought back to the Emergency Room because of persistent fever, sleepiness, and diarrhea.

This child was born at home, a normal spontaneous delivery at term. Shortly after birth he was found to have congenital syphilis and received adequate therapy at a Norfolk, Virginia, hospital. He walked at one year, but had never talked. He had measles and pertussis at one year of age. There was one brother, aged 7, who was in good health. The mother had been treated for syphilis soon after birth of the patient. The patient ate from the table, but also drank milk from the bottle. The family used water from a pump and had an out-

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door privy. The patient had received diphtheria, tetanus, and pertussis immunizations.

Physical examination at the time of admission to the hospital revealed: temperature 104° F. (rectal), pulse 200, respiration 30, weight 24.5 pounds, and height 34.5 inches. The patient was a well-developed and fairly well-nourished child, who screamed whenever he was handled. He appeared acutely ill. The skin was hot and dry and the patient only moderately dehydrated. The head, eyes, ears, and nose were normal. The tonsils were not enlarged but the pharynx was slightly injected with flecks of white material present on the surface of the soft palate. The neck was supple and the chest clear to auscultation. There was no cardiac enlargement but the rate was rapid, and no murmurs were heard. The abdomen was tense due to the child's crying but both the spleen and liver were palpable. Cervical, axillary, and inguinal lymph nodes were palpable, and described as being small and shotty in character. The reflexes were physiological.

Admission laboratory work showed: urinalysis: 50 c.c., alkaline in reaction, no specific gravity reported, otherwise normal except for a 1 plus albumin. Blood: red blood corpuscles 3,500,000, hemoglobin 8.0 grams, white blood cells, 4,800, polymorphonuclears 58 per cent, eosinophils 1 per cent, lymphocytes 39 per cent, and monocytes 2 per cent. Spinal fluid: total protein 55 mg. per cent, otherwise normal; culture negative. The stools appeared yellow and slimy.

The patient was started immediately on Chloromycetin, 100 mg. every three hours, and subcutaneous fluids. Within forty-eight hours his temperature had returned to normal. During the first two or three days after admission, he continued to cry aloud when touched, but his stools gradually decreased in number. The second day of hospitalization, the patient developed a prolapse of the rectum. Many small (1 mm.) white, evenly spaced ulcers with red borders were seen covering the mucosa. Cultures taken from the ulcers at first grew *P. vulgaris*, but later a non-lactose fermenting, gram-negative bacillus, agglutinating with Salmonella Group C-1 diagnostic serum. The patient was seen in Proctology Clinic, at which time it was determined that the infection involved only the distal 4 cm. of the gastrointestinal tract and a biopsy was taken. This was reported on Feb. 12, 1951, as showing only necrotic debris. All attempts to correct the frequent prolapse of the rectum failed and it persisted throughout the hospital stay. Within a week he seemed much improved. His temperature was normal, his pulse varied between 110 and 120 per minute, and his respirations were around 30 per minute. By this time he had been placed on ferrous sulfate, a soft diet, skimmed lactic acid milk formula, and was continuing to receive Chloromycetin. Twelve days after admission, the stools had become formed and dark and the patient's appetite was variable. He was seen again in Proctology Clinic that day, at which time a biopsy of one of the ulcer sites was taken. This was reported as showing partial ulceration of the mucosal surface and a diffusely hemorrhagic tunica propria. Chloromycetin therapy had been discontinued on the eleventh hospital day; temperature was 98° F. (rectal).

Additional laboratory data: Agglutination reactions, including typhoid H, typhoid B, brucella, and Proteus OX_{19}, were all negative. The heterophil agglutination was positive 1-28 on Feb. 9, 1951, and the titer had risen to 1-56 four days later. A blood smear taken the day after admission showed slight hypochromia, stab cells with toxic granulation, many large phagocytic reticuloendothelial macrophages, and some reduction in platelets. A bone marrow smear showed a hyperplasia of the myeloid series, a slight hypoplasia of the erthyroid series, and an increase of reticuloendothelial macrophages, numerous megakaryocytes, but very little platelet production. The white blood count was 4,100 with 58 per cent neutrophilic granulocytes, 41

Fig. 1.

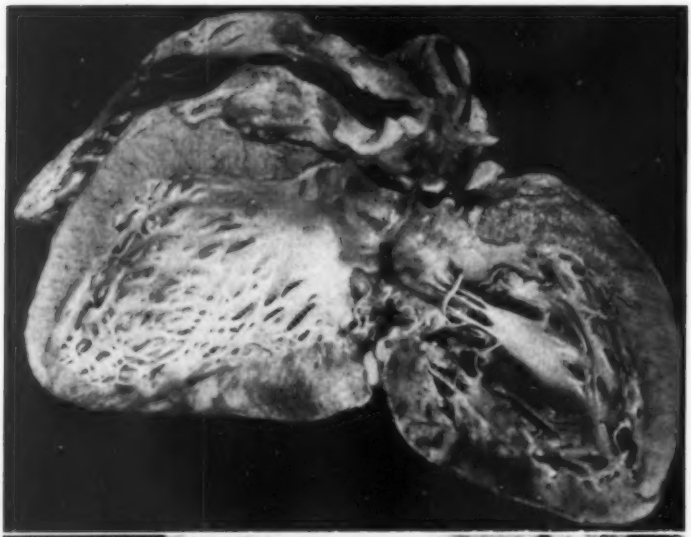

Fig. 2.

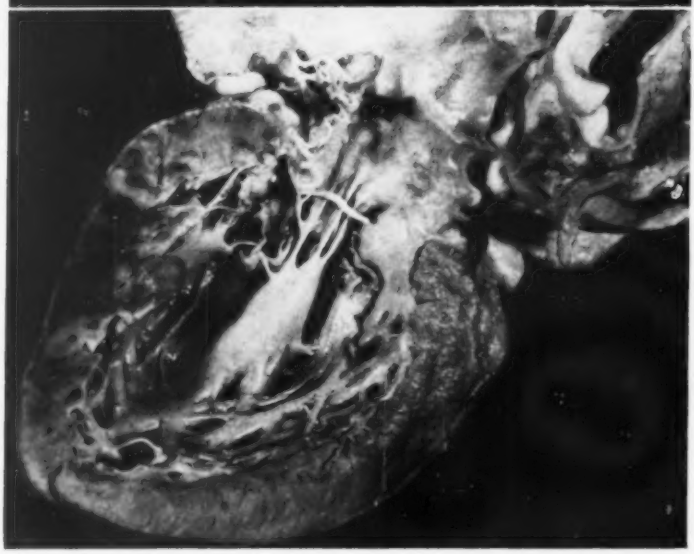

Fig. 1.—Endocardial thickening.

Fig. 2.—A rectangular area of hemorrhagic necrosis is seen in the left myocardium of the posterior wall.

per cent lymphocytes, 1 per cent eosinophilic granulocytes. A blood culture taken the night of admission grew a gram-negative bacillus which agglutinated with Group C-1 Salmonella diagnostic serum.

On the evening of the fifteenth hospital day, the patient's vital signs changed markedly over a twelve-hour period. The temperature rose from 99 to 101° F.; pulse increased from 95 to 125 beats per minute, and respirations slowly increased from 22 to 35 per minute. He spent a fair night on the sixteenth hospital day, and seemed to be doing fairly well. His physical status did not appear to be anything out of the ordinary and his heart showed a rate of 120 with sounds of good quality. There was no evidence of shortness of breath and the patient played throughout the morning. About 3:30 P.M. on Feb. 24, 1951, without warning or outcry, he suddenly succumbed, having seemingly been well five minutes previously. A necropsy was performed four and one-half hours post mortem by Dr. R. K. Waller.*

Pathological Findings.—The body for dissection was that of a 2-year-old, well-developed, thin, Negro male child measuring 34 inches in length. No external abnormalities were present.

The body was opened by a Y-shaped incision, which revealed a fairly well-developed musculature and a panniculus adiposis of 0.5 cm. over the lower abdomen. The pleural and abdominal cavities were free of fluid and adhesions. The mediastinal lymph nodes were prominent. The pericardium contained 20 c.c. of cloudy yellow fluid. The heart weighed 130 grams (normal, 59 grams). A thick shaggy, fibrinous exudate covered the epicardium and was especially prominent over the left ventricle. Multiple petechial hemorrhagic areas, many of which, on section, reached deep into the myocardium almost to the endocardia lining were demonstrated. The myocardium itself was mottled by dark areas alternating with pale ones. A rectangular area of hemorrhagic necrosis, extending from the epicardium to the endocardium occupied a posterior myocardial segment (Fig. 2) on the left ventricle.

The endocardium of the left ventricle was definitely more opaque than normal, obviously due to secondary fibroelastosis (Fig. 1). Both ventricles appeared dilated with the left more marked than the right. The valves appeared normal and the coronary orifices were patent. Microscopically, the epicardium was found to be the seat of an organizing fibrinopurulent exudate. There were areas in which the intramural vessels were completely thrombosed, due to endarteritis obliterans, and a fibroblastic response with newly formed capillaries was visible. The posterior descending branch of the left coronary artery was thrombosed in the segment overlying the infarction of the posterior wall of the left ventricle. The myocardium showed extensive polymorphonuclear infiltration in sections from all chambers (Fig. 3). Focal areas of necrosis and interstitial hemorrhages were seen. In some places, the process appeared to extend into the endocardium and into the papillary muscles. There was edema of the endocardium. Inspection of the valves failed to reveal any evidence of endocarditis. Gram stains of numerous sections revealed occasional gram-negative organisms in the myocardium, of the left ventricle. No organisms were demonstrated in the right ventricular myocardium.

The lungs weighed 230 grams. Their surfaces were slightly bluish-red in color and mottled. On section, a small amount of frothy yellow fluid exuded from the cut surfaces. The tracheobronchial tree was not remarkable but the tracheobronchial lymph nodes were prominent. Microscopically, the visceral pleura revealed no abnormalities. There was some moderate dilatation of the alveolar capillaries and occasional serous exudation into the alveolar lumina. Many of the pulmonary arteries were occluded by recanalized

*Killed in automobile accident, July, 1952.

thrombi and there was intimal proliferation as well as adventitial fibrosis. Bronchi and bronchioles were not remarkable.

The liver weighed 530 grams (normal, 418). Its lower edge was at the level of the right iliac spine. It was mottled, bluish red in color, and, on cross section, showed several irregular bluish red, sharply demarcated areas. In addition, there were one or two subcapsular areas which were light yellowish tan and less sharply demarcated. The liver parenchyma was fairly soft and the markings were indistinct. Microscopically, the capsule was not remarkable. The sinusoids were dilated. There were occasional microabscesses in the midzone of the hepatic lobules. These contained polymorphonuclear leukocytes predominately, many of which were undergoing karyorrhexis.

The spleen weighed 80 grams (normal, 37 grams). The capsule was not thickened. The parenchyma was very firm, and the follicles were prominent. Microscopically, the capsule was not remarkable. The sinusoids were dilated, filled with many polymorphonuclear leukocytes. The endothelial cells lining the sinusoids were somewhat prominent. Enlargement of the malpighian corpuscles was striking and their centers contained large macrophages and necrotic debris. In the periphery of the corpuscles were many normoblasts and myelocytes, while surrounding the small arteries were many chronic inflammatory cells. The walls of the blood vessels were thickened.

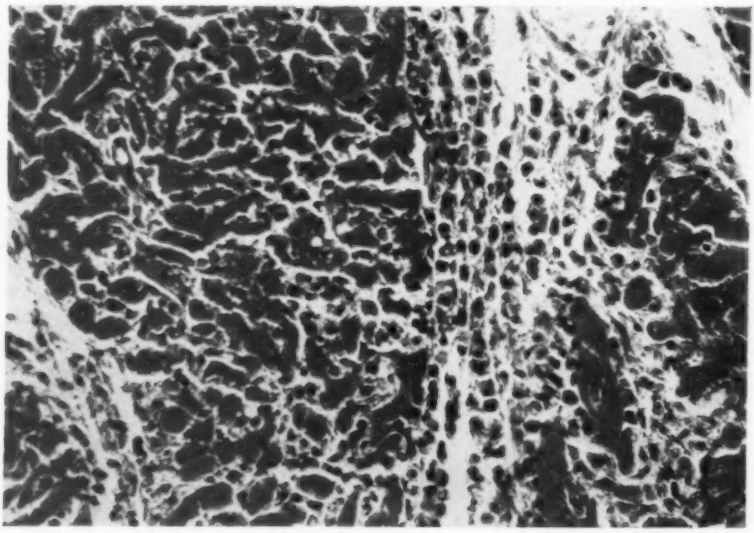

Fig. 3.—Heart. Polymorphonuclear cell infiltration and necrosis of myofibrils evident.

Each kidney weighed 98 grams. The corticomedullary junctions were indistinct and the cortices were mottled and yellowish in color. The capsules stripped with ease, revealing a smooth cortical surface marked by fetal lobulation. The capsules seemed to be under increased tension, but the cortices bulged only slightly after sectioning. Pelves, ureters, and bladder were not remarkable. Microscopically, occasional glomeruli retained their fetal appearance. Some of them contained hyalin thrombi but the Bowman's capsules were not remarkable. A collection of lymphocytes surrounding a glomerulus and tubules were seen in one area.

Some eosinophilic hyalin casts were seen in the distal convoluted tubules.

The gastrointestinal tract was grossly normal. However, several Peyer's patches were slightly enlarged but not ulcerated. They appeared injected and dull reddish brown in color. The large intestine was studded with enlarged lymphoid follicles, particularly in the cecal area. Cup-shaped lymphoid follicles were present in the last 4 cm. of the rectum. The mucosa was slightly raised in this area and there were several areas of ulceration, 7 mm. in diameter. On section, the mucosa and free areas were markedly thickened and hemorrhagic. Microscopic examination revealed hypertrophy and minimal necrosis of Peyer's patches. In the large intestine the mucosal epithelium appeared partially denuded of normal mucosal glands. Many chronic inflammatory cells were seen in the stroma, and in one such area there was a large group of confluent lymphoid follicles which had elevated the mucosa. The mucosa in that area was denuded. The mesenteric lymph nodes were extremely enlarged and brownish red in color. On microscopic examination the sinusoids were widened as if they had previously contained edema fluid. Many acute inflammatory cells were seen in the sinusoids, and erythrocytosis seemed to be present. The follicles, which were prominent, contained some polymorphonuclear leukocytes undergoing necrosis and some macrophages. The remainder of the organs, including the brain, appeared normal, both grossly and microscopically.

Anatomical Diagnosis.—Salmonellosis due to a Group C-1 organism; acute pericarditis, epicarditis, myocarditis, and endocarditis with overwhelming involvement of the myocardium; acute and subacute coronary arteritis; thrombosis posterior descending branch of the left coronary artery; hepatosplenomegaly; generalized lymphocytic tissue enlargement with necrosis of germinal centers; microscopic pulmonary artery embolism without infarction; proctitis; and rectal prolapse. Focal microabscesses of liver. Acute splenic tumor (acute toxic splenitis). Acute and subacute enterocolitis.

DISCUSSION

The incidence of Salmonella infections has been found to be greatest among the aged and very young. In the cases reviewed by Seligmann, Saphra, and Wassermann,[2] children were found to play a major role in the epidemiology. They reported that children under 10 years of age accounted for 40 per cent of all cases, while among infants alone there was a 17 per cent incidence. It was found that there was no marked difference in the rate of occurrence on the basis of type of organism or sex of the patients.

The C-1 group of Salmonella organisms is composed of the following genera[2]:

1. *Salmonella paratyphi C*
2. *Salmonella choleraesuis*
3. *Salmonella thompson*
4. *Salmonella virchow*
5. *Salmonella orangienburg*
6. *Salmonella bareilly*
7. *Salmonella hartford*
8. *Salmonella montevideo*
9. *Salmonella amersfoort*
10. *Salmonella tennessee*
11. *Salmonella georgia*

Of these eleven genera, *S. choleraesuis, S. orangienburg,* and *S. montevideo* are the most common infectious agents in man, while *S. choleraesuis* (26 per cent) and *S. orangienburg* (6.1 per cent) are the most fatal.[2] Since at the Medical College of Virginia Hospital the clinical bacteriological unit uses only Salmonella group diagnostic sera in identifying organisms from cultures of blood and fecal specimens, the genera of C-1 organisms isolated from this case were not identified.

For many years it had been observed that although the Salmonella group of organisms were primarily enteric pathogens, they were capable of producing various disease processes. Several classifications of the clinical syndrome have been made. Probably the most recent and concise, however, was presented by Shulman in 1947.[3] His classification is as follows: (1) typhoidlike infection, (2) gastroenteritis or enterocolitis, and (3) sepsis with bacteremia with or without localization. The fact that sepsis was often secondary to the enteric type of infection allowed the predication that it was responsible for the parenteral complications that developed.

Wells's[1] report dealt with the incidence of endocarditis complicating a case of *S. paratyphi B* infection. He wrote that: "In but one of these 320 cases was endocarditis observed as a complication, nor was endocarditis observed in numerous other single autopsies or smaller series, indicating that, like typhoid, although a bacteremic disease, paratyphoid does not often lead to infection of the heart valves." He was of the opinion that due to their apparently greater pyogenic tendency, paratyphoid infections might play a greater role in producing endocarditis.

Shulman[3] published a review of the cardiac complications of salmonellosis in 1947. His study of the English literature revealed that only sixteen cases of cardiac localization had been reported to that time. Later he reported an additional case. The types of cardiac complications reported by Shulman are: twelve cases with acute bacterial endocarditis, three cases of subacute bacterial endocarditis, and one case of acute pericarditis. The mortality in this series was 82.5 per cent.

An interesting recent article is that of Barnett and Zimmerman[4] who reported a 48-year-old white man who died as a result of coronary arteritis with fatal thrombosis due to *S. choleraesuis*. The case was characterized by myocardial infarction as was our case. In both cases there was involvement of the coronary artery. It is not clear whether the histological changes in Barnett and Zimmerman's case were due entirely or in part to the coronary arteritis especially since it was not stated whether numerous sections were studied from all parts of the myocardium; hence we feel that it is not clear whether the acute myocarditis was established as infectious or ischemic in nature. Polymorphonuclear leukocyte response is seen in early coronary insufficiency as well as acute infections of the myocardium. It is essential to study sections of myocardium taken at a distance from that served by the affected coronary artery. In the case reported here there was a myocardial infarction in the posterior wall of the left ventricle and sections of the entire left ventricular myocardium revealed inflammatory cell infiltration; furthermore, bacterial stains revealed the presence of unmistakable gram-negative bacteria in the myocardium. An intriguing thought is the susceptibility of the coronary arteries to involvement by the Salmonella group of organisms as in the case of Barnett and Zimmerman and the one reported here.

The differential diagnosis included acute rheumatic carditis, isolated nonspecific myocarditis, congenital fibroelastosis, sickle-cell disease, and glycogenic infiltration of the myocardium.

SUMMARY

1. A case of pancarditis due to a Salmonella organism has been reported and is believed to be the first such case.

2. The diagnosis was substantiated by the clinical history of fever, granulocytopenia, and severe diarrhea with the isolation of a gram-negative organism, typed Salmonella C-1 from the stool.

3. A positive blood culture was obtained.

4. The autopsy findings are presented.

5. A gram-negative organism was demonstrated in histological sections of the myocardium.

We wish to express our indebtedness to the Armed Forces Institute of Pathology, Washington, D. C., for their assistance in the study of this case.

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THE TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN

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DATA continue to accumulate concerning the favorable therapeutic effect of streptomycin on tuberculous meningitis in children. In most of these studies streptomycin has been used in conjunction with either Promizole or para-aminosalicylic acid. These results, however, have been far short of the desired goal and all promising new additions to the therapeutic armamentarium, e.g., isoniazid, deserve a thorough clinical trial.

In a previous paper[1] attention was called to Brailey's[2] work, showing that Negro children with tuberculous infection bear a more serious prognosis than do white. It was suggested that the same prognostic difference might also apply to Negro and white children with tuberculous meningitis. This study, then, will deal mainly with a relatively large number of Negro children with tuberculous meningitis, with an attempt at comparison of the results obtained in a much smaller group of white children treated in the same manner.

RESULTS

Since October, 1947, forty* patients (thirty-four Negro and six white) with tuberculous meningitis have been treated on the pediatric service of the Medical College of Virginia Hospitals. Eighteen (45 per cent) of these are surviving at least six months after treatment was begun. Thirteen of these are Negro and five are white. Eight (no recent follow-up on three) of the survivors are living more than three years and one of these is apparently well five and one-half years later.*

Three of the five living white patients are apparently well after more than three years. Another case was diagnosed and treated for one month at another hospital. When admitted to the Medical College of Virginia Hospital he had already developed hydrocephalus and was semicomatose. After one month he was returned to the original hospital with his condition unchanged. The remaining patient in this group was known to have tuberculosis of the hip of two years' duration and was treated in the terminal stage. He lived only eighteen days after therapy was begun.

TREATMENT

In general, the treatment used was a modification of that suggested by Lincoln and Kirmse.[3, 4, 5] Intramuscular streptomycin or dihydrostreptomycin was given in dosage of 20 to 40 mg. per pound of body weight per day over a six-month period. A course of intrathecal streptomycin consisted

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Rimifon (isoniazid) used in this study was furnished by Hoffmann-LaRoche, Inc., Nutley, N. J.

*Includes all admissions prior to January 1, 1953, and one private patient of Dr. Hubert T. Dougan, treated at Johnston-Willis Hospital.

*All statistics as of June 15, 1953.

of forty injections of 25 to 100 mg. each over a period of nine weeks or less. Lately, there has been an attempt to decrease or completely eliminate intrathecal streptomycin therapy.

Promizole was given in dosage sufficient to maintain a blood level of 1 to 3 mg. per cent. For an 18-month-old infant this usually required dosage of 0.5 Gm. every six hours per os. Our original aim was to continue this drug for a period of three years, but this has not usually been accomplished. More recently there has been some tendency toward the substitution of PAS for Promizole.

The last seven cases in this series have had the added benefit of treatment with isoniazid. Dosage for this drug was 4 mg. per kilogram of body weight per day and this has since been increased to 8 mg. Our aim is to continue this medication for about six months. These cases will be discussed separately from the others and will be included in a general paper on the use of isoniazid in the treatment of tuberculosis in children which will be published at a later date.

Two patients received intrathecal P.P.D. (purified protein derivative of tuberculin) according to the method described by Cairns, Smith and Vollum.[6] Both of these patients were considered moribund when therapy was instituted. One patient died but the other improved markedly and his spinal fluid is now normal.

TOXICITY

No attempt will be made here to discuss the toxic reactions of streptomycin and Promizole. These were briefly outlined in a previous publication[1] and have been completely and adequately discussed in other reported studies. It does seem noteworthy that six of the eighteen survivors exhibit some degree of deafness. Otherwise, the only known major residual effect was in a patient mentioned later in this report.

The euphoria which accompanies isoniazid therapy is well known. It is also recognized that manic states occasionally occur. One case in our series merits brief discussion.

T. J., a 6-year-old Negro male, was admitted to Dooley Hospital on June 19, 1952, with history of vomiting, headache, and weight loss of three weeks' duration. A diagnosis of tuberculous meningitis was made and the patient was put on a therapeutic regimen consisting of intramuscular streptomycin 0.5 Gm. every twelve hours, PAS 0.5 Gm. every six hours, and isoniazid 8 mg. every six hours. Six days later isoniazid was increased to 16 mg. every six hours.

The patient appeared to have improved slightly and was in good spirits until July 17, 1952. In retrospect it may be said that he had begun to be somewhat manic for the thirty-six hours preceding, but on this particular day he suddenly leaped from the bed and ran across the room into a closed door. He fell to the floor, arose, and ran into the wall, again knocking himself to the floor. He was then returned to bed and threshed wildly about until sedation was given.

From that time forward he lay in semicoma. He could neither see, hear, nor speak. An x-ray of the skull revealed an L-shaped linear fracture 11 inches in length near the midline in the occipital area.

After some weeks there was partial return of auditory function and later the patient was able to speak a few words. He appeared to be completely blind until his demise on Feb. 28, 1953.

COMMENT

Reports on the therapy of tuberculous meningitis are too numerous to consider in detail. Results continue to vary greatly, with the mortality rate in adults much less favorable than that in children. Bunn,[7] for example, reported seventy-eight consecutive cases of tuberculous meningitis in adults, treated with streptomycin, with only eleven survivors after a two-year period. Lincoln and Sifontes[8] reported thirty-five survivors of fifty-two treated children but Perry's[9] well-documented study listed only seven survivors of twenty-six children with tuberculous meningitis.

One major question is raised by this study: Do Negro children with tuberculous meningitis have a poorer prognosis than do white? There appears to be only one other study comprising a comparatively large number of Negro children. Levinson[10] treated fifteen Negro children with tuberculous meningitis and six of these were living three to twelve months after therapy was begun. Two of the four white children in his series survived. Actually, no comparison is possible between the number of Negro and white children treated either by Levinson or by us. However, the marked difference in mortality rates in Negro and white patients in our series is worthy of note (Table I). The survival rate of the thirty-four treated Negro children is 38 per cent (thirteen cases) while the survival rate of the six white patients is 83 per cent (five cases). It should be stated that one of the latter group was discharged from the hospital, to which he was admitted both before and after his one-month stay at the Medical College of Virginia Hospital, to a "vegetative existence." There appears to be no recent knowledge as to his condition.

In view of the marked difference in mortality of Negro and white children with tuberculous meningitis in this series, racial division in future reports seems to be indicated.

The Committee on Therapy[11] advises that isoniazid be used in conjunction with streptomycin and PAS rather than alone, but still recommends the use of streptomycin and PAS as the treatment of choice of most patients with tuberculosis "in view of the toxicity of isoniazid and the uncertainty about the control of isoniazid-resistant strains of tubercle bacilli." No recommendation was made as to the treatment of tuberculous meningitis. The difference in number of patients in this study treated or not treated with isoniazid does not admit statistical comparison (Table II). It is worth while noting that thirty-three patients (twenty-eight Negro and five white) did not have isoniazid added to the therapeutic regimen. Fourteen (42 per cent) are surviving more than six months following the institution of treatment. Of the seven patients (six Negro and one white) who received isoniazid in addition to streptomycin and PAS four (57 per cent) are surviving more than six months. One of those who died is reviewed briefly elsewhere in this report. He appeared to be pro-

TABLE I. MORTALITY AFTER RACIAL DIVISION

	WHITE	NEGRO	BOTH
Surviving	5	13	18
Died	1	21	22
Total	6	34	40

TABLE II. MORTALITY OF PATIENTS WHEN ISONIAZID WAS ADDED TO TREATMENT

	LIVING	DIED	TOTALS
With isoniazid added	4	3	7
Without isoniazid	14	19	33

gressing satisfactorily until he suffered severe injury during a manic spell, presumably as a result of isoniazid therapy. The other patient who succumbed did not have the benefit of isoniazid therapy until late in the course of his disease. Addition of this drug did not appear to alter his disease in any way.

When isoniazid therapy was introduced, attempt was made to shorten the length of intrathecal streptomycin therapy. All patients treated with isoniazid in this series, however, also received intrathecal streptomycin, the shortest course consisting of fourteen injections.

TABLE III. EFFECT OF MILIARY TUBERCULOSIS ON PROGNOSIS

	MENINGITIS PLUS MILIARY TUBERCULOSIS	WITHOUT MILIARY TUBERCULOSIS
Living	4	14
Died	9	13
Totals	13	27

Finally the prognostic import of miliary tuberculosis should be mentioned (Table III). Miliary tuberculosis was also present in thirteen cases in this series. Of these, only four survived. Of the twenty-seven patients who did not have demonstrable miliary tuberculosis, fourteen are living. As emphasized by Bunn[12] and as suggested by us in a previous paper,[1] the additional presence of miliary tuberculosis seems to lead to increased mortality. It should be noted, however, that of three patients treated with isoniazid, who had miliary tuberculosis in addition to tuberculous meningitis, two are surviving more than six months later.

SUMMARY

Of forty cases of tuberculous meningitis in children, eighteen (45 per cent) survive. The marked difference in mortality of white and Negro children in this series suggests that Negro children bear a more serious prognosis, although the paucity of white children does not allow statistical comparison. The addition of isoniazid to the therapeutic armamentarium seems to be helpful. Those patients who have miliary tuberculosis in addition to tuberculous meningitis have a worse prognosis.

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THERAPEUTIC DOSES OF GAMMA GLOBULIN IN THE TREATMENT OF MEASLES ENCEPHALITIS AND ENCEPHALOMYELITIS

I. A Clinical Study of Forty-One Cases With Follow-up Studies

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THE therapy of measles encephalitis and measles encephalomyelitis has been as varied as the course of the disease and its prognosis. The armamentarium has included parenteral whole blood, pooled blood, pooled serum, convalescent measles serum, and placental gamma globulin. All have been accepted and used with good results in most cases in the prophylaxis and treatment of measles and in the treatment of measles encephalitis and encephalomyelitis. A comprehensive bibliography regarding the administration of these blood substances in measles may be compiled from the extensive list of references in the papers of McKhann,[1] Holroyd,[2] and Janeway.[3] McKhann's careful clinical evaluation of placental gamma globulin in measles prophylaxis gave impetus to the studies of serum gamma globulin.

In 1944 a series of papers was published reporting chemical, clinical and immunologic studies of gamma globulin.† Its physical and chemical characteristics were analyzed by Cohn and his co-workers.[4] Enders and his colleagues[5] found that the gamma globulin fraction carries measles antibodies as well as other antibodies and that these antibodies are concentrated fifteen to thirty times as much as in pooled plasma. Stokes, Maris, and Gellis[6] showed that the degree of protection conferred was increased as the dose of gamma globulin was increased. When a dose as large as 4 or 5 c.c. of gamma globulin was administered to forty patients whose ages varied from 1 to 12 years and who were exposed within a definite interval of time, thirty-nine did not contract measles. Ordman, Jennings, and Janeway,[7] in the same series of papers, noted that the passive immunity conferred by gamma globulin lasted for at least two weeks but not as long as seven to ten weeks since the majority of a series of previously protected boys who were subsequently re-exposed developed average measles. In 1944, the American Medical Association[8, 9] announced that the gamma globulin fraction made from human serum in excess of the requirements of the Armed Forces was being made available for civilian use and the Council on Pharmacy and Chemistry[10] declared in 1946 that this gamma globulin fraction was the most potent prophylactic yet developed against measles. Following this, reports of cases of

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†In this report, unless otherwise designated, *gamma globulin* will be used to indicate the gamma globulin fraction derived from pooled, normal human serum.

measles encephalitis and encephalomyelitis treated with therapeutic doses of human serum gamma globulin began to appear in the literature with increasing frequency.

Hoyne and Slotkowski[11] in 1947 used 40 c.c. of gamma globulin for a critically ill patient, but were undecided as to whether the gamma serum intrathecally, intravenously, and intramuscularly, but stated that there was no evidence of its efficacy. In reporting a series of seventeen cases of measles encephalomyelitis in 1949, Jacobsson and Holmgren[13] stated that gamma globulin (40 c.c.) and convalescent serum (20 to 100 c.c.) had been tried without any effect although, on the whole, their

TABLE I. LITERATURE SURVEY OF OUTCOME OF MEASLES ENCEPHALITIS AND ENCEPHALOMYELITIS CASES

AUTHORS	YEAR	NUMBER OF CASES					PER CENT OF CASES			
		PRESENTED OR REVIEWED	DEATHS	RECOVERY	SEQUELAE	NOT RECORDED OR FOLLOWED	DEATHS	RECOVERY	SEQUELAE	NOT RECORDED OR FOLLOWED
Ford[21]	1928	127	12	51	62	2	9	40	49	2
Peterman and Fox[22]	1939	27	9	17	1	0	33	63	4	0
Geiger and Sappington[23]	1940	13	5	4	4	0	38	31	31	0
Hamilton and Hanna[24]	1941	44	11	24	5	4	25	55	11	9
Neal[25]	1942	81	11	51	19	0	14	63	23	0
Roos[26]	1942	18	1	16	1	0	6	88	6	0
Litvak, Sands, and Gibel[27]	1943	56	8	10	22	16	14	18	39	29
Reisman and Rosen[28]	1943	20	2	8	2	8	10	40	10	40
Hoyne and Slotkowski[11]	1947	20	3	16	1	0	15	80	5	0
Appelbaum, Dolgopol, and Dolgin[14]	1949	74	7	42	25	0	9	57	34	0
Jacobsson and Holmgren[13]	1949	17	2	13	1	1	12	76	6	6
Sawchuk, and associates[29]	1949	50	16	3	19	12	32	6	38	24
Seagle[30]	1949	12	1	7	4	0	8	59	33	0
Spragins, Shinners, and Rochester[31]	1950	31	2	4	12	13	6	13	39	42
Total		590	90	266	178	56	15			

globulin or measles convalescent serum used in other cases had any beneficial effect. They also used pooled plasma (250 to 1,250 c.c.) for almost all of their patients. Compared to previous reports (Table I) their results were favorable. In outlining a clinical procedure for treating measles encephalitis, Litvak[12] in 1947 advocated the use of gamma globulin or convalescent measles clinical results appeared good (Table I). Moreover, weekly electroencephalograms disclosed by the end of four weeks that eleven out of fourteen patients had normal tracings. Appelbaum, Dolgopol, and Dolgin[14] in 1949 reported the use of gamma globulin (amount not stated) in one case with favorable outcome. They concluded that gamma globulin deserved further clinical trial for its

proper therapeutic evaluation. Holliday[15] in 1950 reported the case of an acutely ill 16-month-old child who received 30 c.c. of gamma globulin which was followed by clinical improvement on the third hospital day. No abnormalities were found when the infant was discharged from the hospital twelve days later. Hoffman[16] in 1950 recorded the use of 10 c.c. of gamma globulin in a 7-year-old patient who died twelve hours after admission. The case of a 4-year-old patient who was given 10 c.c. of gamma globulin daily but died two and one-half days after admission was reported by Larsen[17] in 1950. In 1951 Smith[18] treated with 6 c.c. of gamma globulin a 19-month-old infant who developed an attenuated attack of measles encephalitis, the mild nature of which Smith ascribed to the injection of 0.63 c.c. of gamma globulin fifteen days before the onset of the rash. The child was discharged on the third hospital day and an examination ten days later showed that the infant was entirely normal. Jack and his associates[19] in 1952 administered gamma globulin (amount not stated) to three patients with measles encephalitis. One of their critically ill patients, a 5½-year-old child, hospitalized for sixty-three days, received 10 c.c. of gamma globulin and 300 c.c. of pooled irradiated plasma which is equivalent to a total of about 22 c.c. of gamma globulin. This patient seemed normal in all respects seven and one-half months later. Jack and co-workers, however, did not believe there was any evidence that either the gamma globulin or the pooled irradiated plasma was helpful.

ETIOLOGY OF MEASLES ENCEPHALITIS AND ENCEPHALOMYELITIS

Why does encephalitis, with or without myelitic and meningeal involvement occur in only a small percentage of measles cases—in less than 0.3 per cent?* In general, viruses do not easily penetrate the central nervous system's series of defenses. During the years when encephalitis and encephalomyelitis as complications of measles gained increasing recognition several theories were propounded to explain the involvement of the central nervous system. These theories were: (1) the measles virus acquires neurotropic characteristics; (2) some latent virus is activated by the primary disease; (3) toxins in the central nervous system produce the encephalitis; (4) the encephalitis is an allergic or anaphylactic reaction to the measles virus which may be the sensitizing agent. Although these theories are often mentioned and discussed, many authors agree there is no definite evidence to support any of them. We are suggesting several additional hypotheses which either singly or collectively may explain the rare occurrence of encephalitis or encephalomyelitis as the complication of measles. These are:

(1) Because of a previously poor nutritional state, fever, and general debility from the attack of measles, the hematoencephalic barrier becomes weakened, or more permeable, resulting in the invasion of the central nervous system by the virus. This point will be further discussed in a second paper in light of our

*This is the percentage of measles patients who developed encephalitis or encephalomyelitis in the Borough of Brooklyn in New York City during the period of July 1, 1951, to June 31, 1952.

laboratory findings in the blood and cerebrospinal fluid.

(2) The patient does not have the physical ability to produce sufficient antibodies to keep pace with the number of invading or incubating viruses, i.e., he does not have the faculty to develop the necessary acquired immunity as rapidly as occurs in over 99.7 per cent of the cases of measles.

(3) There are rare individuals who cannot establish acquired immunity due to an inability to produce antibodies. An excellent example, recently described by Bruton,[20] is the case of a child whose clinical history was indicative of inability to produce antibodies. This patient's electrophoretic pattern demonstrated the absence of gamma globulin from his blood.

(4) The possibility that the antibodies, which are most probably protein substances or compounds having an affinity for a protein molecule, are destroyed more rapidly than they are formed because of the anteceding fever; the relatively high electric moment of gamma globulin greatly predisposing toward the interaction of gamma globulin with other proteins or smaller molecules (Cohn[4]); or other reasons. Under these conditions of antibody destruction the virus may be able to invade the central nervous system.

FACTORS CONSIDERED IN GAMMA GLOBULIN THERAPY

To obtain 100 per cent cures in measles encephalitis and encephalomyelitis may be unattainable inasmuch as most of the patients are admitted to the hospital when the neurological signs are already present, indicating that the measles virus has already invaded the central nervous system. There are, however, a few patients who are admitted as severe measles cases who soon develop signs of central nervous system involvement. Since the encephalitis or encephalomyelitis is almost always present when these patients are admitted, the goal of therapy is: (1) to reduce the mortality rate; (2) to reduce the incidence of sequelae; and (3) to lessen the severity of sequelae.

These objectives can be achieved by shortening the duration of the acute phase of the illness.

In order to accomplish this and minimize the damage to the central nervous system as much and as rapidly as possible, in addition to adjunctive therapy, large doses of gamma globulin were given. This induces a state of passive immunity wherein either all the virus is neutralized by the antibodies in the gamma globulin or at most only a relatively small amount of virus remains which is insufficient to cause further extensive damage to the nerve tissue. The small residual amount of virus, nevertheless, may be sufficient in susceptible children to evoke a recurrence of the neurological symptoms (as will be illustrated by some of our case histories). Therefore, depending on the response of the patient, successive doses of gamma globulin were administered until the acute phase subsided. The recovery phase was manifested by the patient coming out of coma or stupor, the temperature, pulse, and respirations returning to normal, the neurological signs gradually disappearing, the abnormalities in the cerebrospinal fluid values reverting to normal, and the leukocyte count of the blood returning to normal.

As with other forms of therapy successive doses of gamma globulin rather than a single dosage are necessary because a number of variable factors must be considered in order to obtain complete passive immunity. Janeway[3] has analyzed these factors and has detailed them into two groups: (1) the quantitative and (2) the qualitative. The quantitative factors include (a) the concentration of antibody in the patient determined by the concentration of antibody in the immunizing agent, the size of the dose, the size of the patient, the speed of absorption, the rate of destruction of antibody in the body, (b) the concentration of antibody necessary for neutralization of the virus, toxin, or bacterium producing the disease, and (c) the time of administration of the antibody in relation to the patient's exposure and length of incubation period. Under the heading of qualitative factors Janeway considers the nature of the infectious agent and the pathogenesis of the disease influenced by (a) the portal of entry, (b) sites of multiplication, (c) incubation period, (d) route of spread, and (e) the stage at which the disease can be recognized. To Janeway's list, we may also add in measles encephalitis and encephalomyelitis: (a) the rate of absorption of antibodies into the central nervous system, (b) the concentration of the virus in the central nervous system, (c) the rate of destruction of the antibodies in the central nervous system, (d) the general physical condition of the patient, (e) the rate of reincubation of any remaining virus in the blood and in the central nervous system, (f) the ratio of virus in the blood to that in the central nervous system, and (g) the ratio of antibody in the blood to that in the central nervous system.

OUTCOME OF CASES REPORTED IN THE LITERATURE

A review of 590 cases of measles encephalitis and encephalomyelitis reported in the literature (Table I) shows that the mortality rate is about 15 per cent. Of those who recover from the acute illness, a minimum of 40 per cent will have sequelae. The criteria for determining the degree of sequelae vary from observer to observer. Some authors included in their reports careful physical examinations, electroencephalographic studies, and psychiatric evaluations at the time of discharge; some authors continued to follow their patients and reported the follow-up examinations, but others did not publish such detailed data. Furthermore, the terms "recovery" and "sequelae" do not denote complete recovery and permanent sequelae in every series reported. Sometimes recovery merely meant that the patient survived the illness. On the other hand, the appraisal of sequelae, especially in the cases that were not followed, has been often incomplete because the central nervous system is capable of extensive, although not necessarily complete, regeneration in measles encephalitis and encephalomyelitis, which may continue over a period of many months. Single case reports and small series of cases have been omitted from Table I because it was thought that the larger series would give a more representative picture.

As some cases in Table I received parenteral whole blood, while others received pooled blood, pooled serum, convalescent measles serum, placental

gamma globulin, or human immune serum gamma globulin, the precise role of these blood substances is difficult to evaluate.

MATERIAL AND METHODS

In order to illustrate the difference in treatment with and without gamma globulin we have divided our patients into three groups: Group I (Table II)—fourteen patients who received no gamma globulin in the acute phase; Group II (Table III)—twelve patients who received from 4 to 16 c.c. of gamma globulin in the acute phase (a total dosage of from 0.07 to 0.30 c.c. of gamma globulin per pound of body weight); Group III (Table IV)—fifteen patients who received 20 c.c. or more of gamma globulin in the acute phase (a total dosage of from 0.43 to 1.1 c.c. per pound of body weight). We have observed thirty-five cases in the epidemic of 1951-1952. Six other hitherto unreported cases from 1949 and 1950 have been included to exemplify particular points in the treatment of these patients. This has been done with the realization that possibly several strains of measles virus have been responsible for the epidemics.

The gamma globulin used in our cases was obtained from pooled normal human plasma and was administered intramuscularly.

The patients presented in this paper were all critically ill. If the central nervous system complications were of very mild nature the patients were excluded. Cases of measles encephalitis or encephalomyelitis were considered mild when there were no episodes of convulsions or coma during the illness, and when the neurological signs and symptoms were transient or mild.

The onset of encephalitis or encephalomyelitis was from three to seven days after the appearance of the measles rash in forty instances; in the remaining case it was one day after the eruption. The average day of onset for the three groups is remarkably similar, 4.9, 4.8, and 4.9 days, respectively, after the measles rash.

It has been noted by other authors that sex distribution is equal in this illness. Our forty-one patients were also equally divided—twenty males and twenty-one females.

PATIENTS WHO RECEIVED THERAPEUTIC DOSES OF GAMMA GLOBULIN

The case histories of all forty-one patients are given in Tables II, III, and IV; the cerebrospinal fluid and serum findings will be found in the second paper.

Fifteen patients (Group III) received 20 c.c. or more (a total dosage of 0.43 c.c. or more per pound of body weight) in the acute phase. Of these, twelve cases (Cases 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 and 40) made a rapid recovery after the administration of gamma globulin. In order to present a more detailed account of when the successive injections of gamma globulin were given and how soon afterward improvement was noted, four case histories will be briefly narrated. The four cases are: Cases 29 and 35, severe encephalomyelitis, and Cases 31 and 38, severe encephalitis. The three other cases in this group (Cases 28, 39, and 41) will also be described because of further complications or unusual features. For additional information on these cases the reader is referred to Table IV. The effect of large doses of

TABLE II. PATIENTS WHO RECEIVED NO GAMMA GLOBULIN IN THE ACUTE

CASE NO.	MONTH AND YEAR ADMITTED	AGE YEARS	WEIGHT POUNDS	CLINICAL PICTURE	PNEUMONIA	DEGREE OF SEVERITY	TOTAL AMOUNT ANTIBIOTICS AND SULFA DRUGS GIVEN DURING THE NUMBER OF STATED DAYS
1.	6-49	10	68	Vomiting; diplopia; frontal headache; dizziness; drowsiness; speech difficult; pupils sluggish; lack of convergence; abdominals absent; deep reflexes hypoactive; comatose; urinary retention; gamma globulin 17, 18, 19, 20 and 21 days after admission, a total of 45 c.c. of gamma globulin	No	Severe	Streptomycin 5.5 Gm./5.5 Aureomycin 4.4 Gm./8 Penicillin 8,600,000 u./21
2.	7-49	7½	65	Disoriented; convulsions; reflexes hyperactive; comatose; cyanotic	Yes	Severe	Chloromycetin 4.8 Gm./7 Penicillin 2,250,000 u./5 Sulfadiazine 13 Gm./5
3.	5-50	11		Drowsy; lucid; nuchal rigidity; positive Kernig; paresis of both legs; back weakness; hyperactive deep tendon reflexes; absent abdominals; urinary retention	No	Severe	Aureomycin 42 Gm./60
4.	6-50	8		Irritable; nuchal rigidity; stiff back; positive Kernig	No	Moderate	Penicillin 2,100,000 u./6
5.	6-50	2		Convulsions; listless; irritable; hyperactive reflexes; nuchal rigidity	No	Moderate	Penicillin 900,000 u./3
6.	7-51	5	51	Weakness right side; urinary retention; unable to walk; bilateral Babinski; weakness both lower extremities; nuchal rigidity; hypoactive right knee jerk; positive Brudzinski; mentally clear; absent abdominals	No	Moderate	Chloromycetin 10.5 Gm./11
7.	7-51	5		Convulsions; comatose; twitching; nystagmus to left; pupils sluggish; slight cyanosis; twitching left hand; positive Kernig bilateral; positive Brudzinski; nuchal rigidity; positive Babinski bilateral; abdominals absent; convulsion predominantly on left	No	Severe	Crysticillin 2,000,000 u./6 Aqueous penicillin 600,000 u./1
8.	8-51	6	72	Cloudy sensorium; no reaction to stimuli; pupils dilated and not reacting; positive Brudzinski; Babinski on left; abdominals absent; absent knee jerks; drowsy; superficial and deep reflexes absent; vomiting; nuchal rigidity; convulsions	No	Severe	Cysticillin 4,800,000 u./10 Aqueous penicillin 100,000 u./1
9.	8-51	6		Absent knee and ankle jerks; biceps, abdominal and cremasteric rereflexes absent; stuporous; dehydrated; moaning; positive Babinski; some nuchal rigidity; paresis lower extremities; drowsy; right side of mouth drooping	No	Severe	Streptomycin 3.5 Gm./5 Crysticillin 3,900,000 u. 13

PHASE OF MEASLES ENCEPHALITIS AND ENCEPHALOMYELITIS—GROUP 1

ADRENAL HORMONE THERAPY TOTAL AMOUNT DURING NUMBER OF STATED DAYS	TEMP. ABOVE 99.6°F. (RECTAL) DAYS	DAYS IN COMA	FIRST DAY MARKED IMPROVEMENT	HOSPITAL STAY DAYS	CONDITION ON DISCHARGE	CONDITION ON FOLLOW-UP
None	53	4	4	55	Moderate leg weakness; hyperactive knee jerks; ankle clonus; weakness of arms and legs with spasticity	3 years: Right footdrop; some weakness of right hamstring muscles; occasional enuresis; abdominal reflexes absent
None	2	1½	2	12	Motor aphasia; moderate emotional instability with evidence of negativism; moderate spasticity of right hand with mild impairment of ability to use hand; slight right facial weakness	3 years: Private physician reports blank look to face and slow response to questions
None	3	0	44	62	Left ocular paresis; hyperreflexia; decreased abdominals; positive Babinski; weakness of both lower extremities	2 years: Private physician reports increased knee, ankle jerks; otherwise negative
None	3	0	3	8	No apparent residuals	2 years: Complete recovery
None	⅓	0	1	5	No apparent residuals	2 years: Private physician reports complete recovery
None	1	0	5	12	Walks with help; unsteady; left Babinski; weakness lower extremities	1 year: Apparently completely recovered
None	3	3	3	6	Abdominal reflexes absent; urinates once in 24 hours	No report
None	3	0	2	15	Pyramidal and extra-pyramidal symptoms with personality disorganization and scattering of recall and synthesis	3 months: Readmitted for upper respiratory infection; mental and neurological status was only slightly better than on previous discharge 1 year: Apparent complete recovery
None	3	4	4	14	Left supranuclear facial; apprehensive; whining; withdrawal; tendency to reject	10 months: Mild feeding problem; complete recovery 13 months: Complete recovery

TABLE II.—

CASE NO.	MONTH AND YEAR ADMITTED	AGE YEARS	WEIGHT POUNDS	CLINICAL PICTURE	PNEUMONIA	DEGREE OF SEVERITY	TOTAL AMOUNT ANTIBIOTICS AND SULFA DRUGS GIVEN DURING THE NUMBER OF STATED DAYS
10.	12-51	3½	41	Nuchal rigidity; vomiting; positive Brudzinski; irritable; somnolent; dehydrated; right cremasteric less active than left	No	Moderate	Aureomycin 4.1 Gm./8 Streptomycin 7.0 Gm./8 Crysticillin 2,100,000 u./7 Aqueous penicillin 1,800,000 u./2
11.	1-52	1¼		Deep and superficial reflexes cannot be elicited; neck muscles completely atonic; facial paralysis; lethargic; spastic; comatose	Yes	Died	Chloromycetin 0.30 Gm./0.5 Streptomycin 0.75 Gm./0.5 Aqueous penicillin 700,000 u./0.5
12.	2-52	10/12		Convulsions; right facial paralysis; disorientation; right hemiplegia; positive Babinski on right	Yes	Severe	Chloromycetin 3.5 Gm./2 Streptomycin 4.5 Gm./4 Crysticillin 1,500,000 u./1 Aqueous penicillin 2,700,000 u./3 Gantrisin 7.3 Gm./5
13.	2-52	7	48	Lethargic; semicomatose; bilateral Babinski	Yes	Moderate	Dihydrostreptomycin and streptomycin 6.5 Gm./8 Crysticillin 5,700,000 u./10 Aqueous penicillin 1,300,000 u./2
14.	5-52	5		Mental retardation and spasticity due to birth injury; loss of consciousness; hyperactive deep tendon reflexes; bilateral Babinski	No	Moderate	Cysticillin 2,400,000 u./4

gamma globulin on temperature may be found in the temperature curves of this group which are charted in Figs. 1 and 2.

Case 1 of Group I will also be presented because he received large doses of gamma globulin, but not until he had been in the hospital for seventeen days.

CASE 29.—This 7-year-old child was admitted five days after the onset of the measles rash with a temperature of 102.8° F., pulse of 126 per minute, and respirations 36 per minute. He was in coma. He had nystagmus, dilated pupils, and trismus of the jaw. His neck was rigid. There was flaccid quadriplegia. The deep and superficial reflexes were absent. The cerebrospinal fluid contained 30 cells per cubic millimeter, mostly lymphocytes, and 102 mg. total protein per 100 ml. He was given 20 c.c. of gamma globulin on admission and another 20 c.c. seventeen hours later (a

CONT'D

ADRENAL HORMONE THERAPY TOTAL AMOUNT DURING NUMBER OF STATED DAYS	TEMP. ABOVE 99.6°F. (RECTAL) DAYS	DAYS IN COMA	FIRST DAY MARKED IMPROVEMENT	HOSPITAL STAY DAYS	CONDITION ON DISCHARGE	CONDITION ON FOLLOW-UP
None	1½	0	2	8	No paralysis or palsies; positive Babinski on right	5 months: Positive Babinski on right 9 months: Complete recovery
None				½	Deceased 13 hours after admission; temperature spiked to 107.0° F.	
None	5	0	4	53	Definite weakness right; drooping right angle of mouth; bright and playful	3 months: Moderate right hemiparesis; ataxia of right upper extremity; dorsiflexion deformity of right foot 6 months: Face drawn to left on smiling; slight stiffness right foot; slight tension in right upper extremity 9 months: Died during a convulsion
None	6	6	6	15	No apparent neurological abnormalities	2 months: Absent ankle jerks
None	0	⅙	1	5	Cannot be determined	1 month: According to parents child recovered from effects of encephalitis; cannot be determined

total dosage of 0.73 c.c. per pound of body weight). One and one-half days after admission he was responsive and alert, hyperactive, and he attempted to sit up. The neurological examination was normal except for the absence of the abdominal reflexes.

CASE 31.—A child, 13 years old, was admitted in coma with a history of convulsions five days after the eruption of the measles rash. Her temperature was 105.0° F., pulse, 140 per minute, and respirations, 32 per minute. There was positive Kernig and the deep and superficial reflexes were absent. Her cerebrospinal fluid contained 387 cells per cubic millimeter, mostly lymphocytes, 72 mg. total protein per 100 ml., and 2.6 mg. inorganic phosphorus per 100 ml. The patient received 20 c.c. of gamma globulin on admission, and three more injections of 20 c.c. each seventeen, twenty-four, and twenty-four hours apart for a total dose of 80 c.c. in sixty-five hours (a total dosage of 0.7 c.c. of gamma globulin per pound of

TABLE III. PATIENTS WHO RECEIVED 4 TO 16 C.C. OF GAMMA GLOBULIN IN THE

CASE NO.	MONTH AND YEAR ADMITTED	AGE YEARS	WEIGHT POUNDS	CLINICAL PICTURE	PNEUMONIA	DEGREE OF SEVERITY	TOTAL AMOUNT ANTIBIOTICS AND SULFA DRUGS GIVEN DURING THE NUMBER OF STATED DAYS
15.	1-52	3	37	Convulsions; positive Kernig; depressed knee jerks	Yes	Moderate	Aureomycin 4.8 Gm./5 Streptomycin 1.5 Gm./1.5 Aqueous penicillin 1,800,000 u./3
16.	1-52	8		Coma; convulsions; nuchal rigidity; pupils do not react; no corneal reflex	Yes	Severe	Chloromycetin 3.0 Gm./4 Streptomycin 7.0 Gm./8 Crysticillin 1,500,000 u./3 Aqueous penicillin 4,000,000 u./6
17.	2-52	4	40	Developed encephalitis 5 days after admission to hospital; lethargic; drowsy; responding sluggishly to commands; nuchal rigidity; positive Brudzinski; superficial and deep tendon reflexes poorly obtained; unable to sit up; semicomatose; abdominals absent	No	Severe	Streptomycin 3.5 Gm./4 Crysticillin 3,000,00 u./10 Aqueous penicillin 2,800,000 u./4
18.	2-52	6		Lethargic; all reflexes hypoactive; positive Kernig; positive Brudzinski; nuchal rigidity	Yes	Died	Chloromycetin 1.5 Gm./2 Crysticillin 1,200,000 u./2 Streptomycin 1.3 Gm./2
19.	2-52	13	113	Lethargic; well oriented; headache on sitting up; vomiting; nuchal rigidity; pain in back of head; hypoactive superficial and deep reflexes; positive Brudzinski; urinary retention	No	Moderate	Chloromycetin 4.5 Gm./4
20.	3-52	9	87	Convulsions; lethargic; irritable; vomiting; somewhat dehydrated; oriented; alert; nuchal rigidity; exaggerated superficial and deep reflexes; positive Kernig; positive Brudzinski	No	Moderate	Chloromycetin 3.5 Gm./3.5 Crysticillin 300,000 u./1
21.	3-52	7	55	Drowsy; restless; irritable; lethargic; moaning; nuchal rigidity; absent superficial reflexes; positive Brudzinski; incontinent	No	Moderate	Chloromycetin 4.5 Gm./6 Crysticillin 3,000,000 u./5

*In addition to the 10 c.c. of gamma globulin Case 16 also received 250 c.c. whole blood and 550 c.c. plasma which are equivalent to a total of approximately 35 c.c. of gamma globulin. This patient could be included in either Group II or Group III but is tabulated in Group II since we are considering only the blood concentrate, gamma globulin, in Group III.

ACUTE PHASE OF MEASLES ENCEPHALITIS AND ENCEPHALOMYELITIS—GROUP II

GAMMA GLOBULIN TOTAL C.C. DURING NUMBER OF STATED DAYS	ADRENAL HORMONE THERAPY TOTAL AMOUNT DURING NUMBER OF STATED DAYS	TEMP. ABOVE 99.6° F. (RECTAL) DAYS	DAYS IN COMA	FIRST DAY MARKED IMPROVEMENT	HOSPITAL DAYS STAY	CONDITION ON DISCHARGE	CONDITION ON FOLLOW-UP
4/1	None	2	0	2	6	Moderate nuchal rigidity	5 months: No behavior problems; has slight left internal strabismus; ankle clonus right 8 months: Complete recovery
10/2*	Eschatin 16 c.c. /3 ACTH 0.4 Gm./5	8	7	7	22	Oriented but irrational; tremors of lips and extremities while in upright position	4 months: Private physician reports complete recovery
10/1	None	7	12	12	28	Depressed deep tendon reflexes	2 months: Absent ankle jerks; questionable right Babinski; absent biceps jerks 6 months: Complete recovery
8/1	None	2	2			General condition deteriorated rapidly in two days; temp. rose to 104.0° F.; pulse, 160; respiration, 40; became restless with facial grimacing; later aphonic; all extremities became flaccid; died	
8/1	None	2	0	2½	6	Blurring of right optic disc	3 months: Blurring of the right optic disc 7 months: Complete recovery
8/1	None	5	0	5	8	Apparently in good condition; no apparent neurological sequelae	2 months: Emotional; cries easily; occasional temper tantrums; I.Q. very high; slight nystagmus to the left 7 months: Complete recovery
8/1	Cortone 25 mg. /1	3	0	2	7	Hyperactive deep tendon reflexes	3 months: Hyperactive deep tendon reflexes 5 months: Hyperactive knee and ankle jerks; otherwise negative

TABLE III.—

CASE NO.	MONTH AND YEAR ADMITTED	AGE YEARS	WEIGHT POUNDS	CLINICAL PICTURE	PNEUMONIA	DEGREE OF SEVERITY	TOTAL AMOUNT ANTIBIOTICS AND SULFA DRUGS GIVEN DURING THE NUMBER OF STATED DAYS
22.	3-52	8	63	Lethargic; nuchal rigidity; deep and superficial reflexes absent; positive Kernig; positive Brudzinski; positive Babinski; left ankle clonus; comatose	No	Severe	Chloromycetin 14.0 Gm./11 Streptomycin 2.8 Gm./4 Crysticillin 500,000 u./3 Aqueous penicillin 3,100,000 u./4
23.	3-52	5		Posteonvulsive coma; generalized areflexia; eyes dilated; pupils did not react	No	Died	Chloromycetin 0.5 Gm./1 Aqueous-penicillin 600,000 u./1
24.	3-52	2½	33	Drowsy; stuporous; pupils sluggish; responds to stimuli; weakness in left arm; positive Kernig; left positive Babinski; right ankle clonus	No	Severe	Chloromycetin 8.0 Gm./6 Crysticillin 2,500,000 u./1 Aqueous penicillin 4,500,000 u./6
25.	3-52	6	56	Coma; nuchal rigidity; positive Brudzinski; positive Kernig; hyperactive deep tendon reflexes; left ankle clonus	No	Severe	Chloromycetin 41.0 Gm./26 Streptomycin 3.5 Gm./4 Aqueous penicillin 7,600,000 u./15 Crysticillin 18,600,000 u./31
26.	4-52	7		Comatose; pupils dilated; nuchal rigidity; positive Kernig; positive Brudzinski; hyperactive deep tendon reflexes; absent cutaneous reflexes; positive Babinski bilateral	No	Died	Chloromycetin 1 Gm./1 Crysticillin 1,200,000 u./2

body weight). Two and one-half days after admission she started coming out of coma and was looking about her. Her reflexes became more active. She was talking the following day. Three days after admission her temperature was 98.8° F., pulse 70 per minute; and respirations 24 per minute; however, during the next twenty-four hours her temperature rose slowly to 101.0° F., but came down to normal the following day and remained normal thereafter.

CASE 35.—This 10½-year-old child was admitted to the hospital seven days after the appearance of the measles rash with a temperature of 101.0° F. which soon rose to 103.4° F. Her pulse was 130 per minute and her respirations were 22 per minute. The fundi were congested; there was nuchal rigidity; the deep and superficial reflexes were hyperactive; the Kernig, Babinski, and Brudzinski signs were positive. She had a headache. There was urinary retention. The following day her legs were flaccid and exquisitely painful. On admission her cerebrospinal fluid had 188 cells per cubic millimeter, mostly lymphocytes,

CONT'D

GAMMA GLOBULIN TOTAL C.C. DURING NUMBER OF STATED DAYS	ADRENAL HORMONE THERAPY TOTAL AMOUNT DURING NUMBER OF STATED DAYS	TEMP. ABOVE 99.6° F. (RECTAL) DAYS	DAYS IN COMA	FIRST DAY MARKED IMPROVEMENT	HOSPITAL STAY DAYS	CONDITION ON DISCHARGE	CONDITION ON FOLLOW-UP
16/2	Cortone 100 mg./2	9	7	7	13	Flaccid paralysis both lower extremities; sluggish reflexes both lower extremities	1 month: Left lower extremity slightly weaker than right; walks with assistance; left knee jerk diminished; bilateral ankle clonus; bilateral Babinski 5 months: Pupils react sluggishly; right knee jerk hyperactive; right ankle clonus; abdominal reflexes only occasionally elicited; no difficulty in walking; right positive Babinski
4/1	Cortisone 50 mg./1					Child admitted in convulsions; temp. 109.0° F.; died 2½ hours after admission	
10/1	None	2	5	5	12	Dilated pupils	1 month: Pupils dilated; otherwise negative 5 months: Complete recovery
8/1	None	6	18	18	62	Weakness upper and lower extremities, more on right; rigidity of neck and spine; hyperreflexia; positive Babinski; ankle clonus; absent abdominals; moderate mental retardation	7 weeks: Positive Babinski on left and doubtful on right; slight stiffness in gait; complete mental recovery
14/2	None	2	2			In course of 2 days temp. rose to 104.6° F.; pulse, 192; respirations to 48, and child died in coma	

132 mg. total protein per 100 ml., and 2.2 mg. inorganic phosphorus per 100 ml. The patient received 20 c.c. of gamma globulin on admission, another 20 c.c. twelve hours later, and 10 c.c. twenty-one hours after the second injection, making a total of 50 c.c. in thirty-three hours (a total dosage of 0.8 c.c. of gamma globulin per pound of body weight). Three and one-half days after admission her temperature was 97.4° F., pulse 96 per minute, and respirations 20 per minute, and stayed normal thereafter. Five days after admission there was improvement; There was increased muscle strength in the lower extremities and the pain was subsiding. Eight days after admission there was no apparent muscle weakness although the reflexes were slightly depressed.

CASE 38.—A 9½-year-old child was admitted with a history of convulsions seven days after the eruption of the measles rash. The neurological examination on admission disclosed a comatose child with dilated pupils, mild papilledema, and positive Kernig and Babinski signs. The abdominal reflexes were absent. Her tempera-

TABLE IV. PATIENTS WHO RECEIVED 20 C.C. OR MORE OF GAMMA GLOBULIN IN THE ACUTE

CASE NO.	MONTH AND YEAR ADMITTED	AGE YEARS	WEIGHT POUNDS	CLINICAL PICTURE	PNEUMONIA	DEGREE OF SEVERITY	TOTAL AMOUNT ANTIBIOTICS AND SULFA DRUGS GIVEN DURING THE NUMBER OF STATED DAYS
27.	8-50	6		Convulsions; stupor; somewhat irrational; depressed deep tendon reflexes; Babinski on right; Oppenheim on right; sluggish abdominals; nuchal rigidity	No	Moderate	None
28.	2-52	5½		Convulsions; tremors; pupils dilated and fixed; coma	No	Severe	Chloromycetin 6.0 Gm./2 Streptomycin 4.7 Gm./5 Crysticillin 1,500,000 u./2 Aqueous penicillin 2,300,000 u./3
29.	4-52	7		Comatose; nuchal rigidity; flaccid quadriplegia; deep and superficial reflexes absent; nystagmus; dilated pupils; trismus of jaw	No	Severe	Chloromycetin 16.8 Gm./6 Crysticillin 900,000 u./3
30.	4-52	8	72	Stuporous; deep and superficial reflexes absent; positive Kernig; positive Brudzinski; nuchal rigidity; absent abdominals, convulsions	No	Severe	Chloromycetin 12.3 Gm./9 Crysticillin 5,400,000 u./9
31.	4-52	13	118	Comatose; deep and superficial reflexes absent; positive Kernig; headache; convulsions; complete areflexia	No	Severe	Chloromycetin 14.0 Gm./7 Crysticillin 5,400,000 u./9
32.	4-52	4		Generalized convulsions; coma; right hemiplegia; throat full of mucus; complete areflexia	No	Severe	Chloromycetin 11.0 Gm./5 Penicillin 1,700,000 u./3 Streptomycin 3.0 Gm./3 Gantrisin 19.5 Gm./5
33.	4-52	5½	49	Convulsions; coma; twitching of arms and face; neck and extremities flaccid; positive Babinski; cyanosis; responds to painful stimuli only	No	Severe	Chloromycetin 7.8 Gm./3 Crysticillin 3,600,000 u./2 Aqueous penicillin 600,000 u./1
34.	4-52	5	55	Severe headache; convulsions; stupor; delirium; fundi congested; all reflexes hyperactive; ankle clonus; positive Babinski; positive Brudzinski	No	Severe	Chloromycetin 9.8 Gm./4 Streptomycin 1.0 Gm./1

*Antibiotics were started on the third hospital day at the time of onset of the cellulitis.

†Exact duration of the temperature is not known because patient was transferred to another hospital for possible neurosurgery.

‡Fever was continuous during the first 77 days and intermittent during the following 53 days.

GAMMA GLOBULIN TOTAL C.C. DURING NUMBER OF STATED DAYS	ADRENAL HORMONE THERAPY TOTAL AMOUNT DURING NUMBER OF STATED DAYS	TEMP. ABOVE 99.6° F. (RECTAL) DAYS	DAYS IN COMA	FIRST DAY MARKED IMPROVEMENT	HOSPITAL STAY DAYS	CONDITION ON DISCHARGE	CONDITION ON FOLLOW-UP
20/1	None	⅓	0	1	5	No apparent residuals	2 years: No behavior problem; minimal weakness of left external rectus
20/1	Adrenal cortex extract 12 c.c. /1	6	5	5	55	Right hemiparesis; right supranuclear facial weakness	2 months: Speech defect; right hemiparesis; some wasting of calf and plantar muscles on right; deep reflexes on right increased; diminution of right abdominal reflexes; plantar response absent on right; right central facial weakness; right corneal reflexes diminished; depressed pain sensation on right 6 months: Right temporal hemianopia; right hemiparesis with hyperactive reflexes; gait is spastic; right hand is spastic but can be extended fully; speech coherent
40/1	None	1½	2	2	7	Apparently completely recovered	5 months: Private physician reports complete recovery
80/3	None	3	0	4	12	Apparently completely recovered	3 weeks: No problems in behavior; absent light reflex in right eye 5 months: Complete recovery
80/3	None	4	2½	2½	12	Apparently completely recovered	1 month: Complete recovery
20/1	Adrenal cortex extract 30 c.c. /2	2	1	1	13	Apparently completely recovered	5 months: Complete recovery
40/2	None	1	⅓	1	11	Congested fundi; right Babinski	2 weeks: Alert; intelligent; nightmares and enuresis; pupils dilated; sluggish to light; mild congestion of fundi; right Babinski 5 months: Enuresis once a night; questionable right Babinski
30/1	Adrenal cortex extract 10 c.c. /1	2	1	1	15	Left Babinski	2 weeks: Left Babinski 4 months: Nervous; headaches once a week, otherwise negative

TABLE IV.—

CASE NO.	MONTH AND YEAR ADMITTED	AGE YEARS	WEIGHT POUNDS	CLINICAL PICTURE	PNEUMONIA	DEGREE OF SEVERITY	TOTAL AMOUNT ANTIBIOTICS AND SULFA DRUGS GIVEN DURING THE NUMBER OF STATED DAYS
35.	4-52	10½	66	Headache; anorexia; urinary retention; ocular fundi congested; nuchal rigidity; deep and superficial reflexes hyperactive; positive Babinski; positive Kernik; positive Brudzinski; lower extremities flaccid and painful	No	Severe	Chloromycetin 4.0 Gm./1 Streptomycin 2.0 Gm./2 Crysticillin 300,000 u./1 Gantrisin 2.4 Gm./1
36.	5-52	6½	48	Severe frontal headache; photophobia; nuchal rigidity; stiff back; positive Babinski on right; positive Kernig; positive Brudzinski; papilledema; alert	No	Moderate	Chloromycetin 1.5 Gm./1 Streptomycin 0.5 Gm./1
37.	5-52	3½	31	Convulsions; coma; nystagmus; nuchal rigidity; stiff back; increased deep and superficial reflexes; positive Kernig; positive Brudzinski; ankle clonus	No	Severe	None
38.	5-52	9½	65	Convulsions; coma; dilated pupils; papilledema; positive Kernig; positive Babinski; absent abdominal reflexes	No	Severe	Crysticillin 3,000,000 u./4* Aqueous penicillin 2,000,000 u./3* Chloromycetin 9.0 Gm./5* Aureomycin 9.5 Gm./5*
39.	5-52	5		Stupor; convulsions; vomiting; pupils dilated and sluggish to light; hyperactive knee and ankle jerks; absent abdominals	No	Severe	Crysticillin 3,000,000 u./6 Aqueous penicillin 600,000 u./2
40.	5-52	10	90	Convulsions; pupils dilated; fundi engorged; nuchal rigidity; hyperactive deep tendon reflexes; bilateral Babinski	No	Moderate	None
41.	5-52	7	35	Stupor; whines; pupillary reflexes absent; pupils dilated; nuchal rigidity; hyperactive deep tendon reflexes; abdominal and cremasteric reflexes absent; plantar withdrawal	No	Severe	Chloromycetin 13.5 Gm./7 Terramycin 4.9 Gm./12 Crysticillin 9,000,000 u./15 Aureomycin 10.0 Gm./5

CONT'D

GAMMA GLOBULIN TOTAL C.C. DURING NUMBER OF STATED DAYS	ADRENAL HORMONE THERAPY TOTAL AMOUNT DURING NUMBER OF STATED DAYS	TEMP. ABOVE 99.6° F. (RECTAL) DAYS	DAYS IN COMA	FIRST DAY MARKED IMPROVEMENT	HOSPITAL STAY DAYS	CONDITION ON DISCHARGE	CONDITION ON FOLLOW-UP
50/1½	Adrenal cortex extract 10 c.c. /1	3½	0	7	18	Limp on left; abdominal and ankle reflexes absent	3 weeks: No behavior problems; absent plantar reflexes bilateral 4 months: Questionable left Babinski; gait normal
30/1	None	2½	0	2	13	Apparently completely recovered	1 month: Complete recovery
30/1	None	1	½	½	7	Alert; ankle clonus on right	2 weeks: Complete recovery 5 months: Complete recovery
40/1	Adrenal cortex extract 15 c.c. /3	1	⅓	⅓	22	Pupils dilated; blurred nasal margin of left optic disc; bilateral Babinski	3 weeks: Pupils moderately dilated; questionable bilateral Babinski 5 weeks: Complete recovery 3 months: Complete recovery 5 months: Complete recovery
20/1 Second admission 10/1	None	2½†	5	6	18	Incontinent of urine and feces; does not speak spontaneously but repeats spoken words; remembers nursery rhymes	1 month: Private physician reports complete recovery
46/4	None	1	0	½	6	Mild engorgement of fundi; hyperactive deep tendon reflexes; bilateral Babinski	2 months: Eyegrounds normal; complete recovery
216/23	None	130‡	22	10	192	Some facial masking; drools frequently; incontinent of urine and feces (not completely toilet trained for urine and feces at the time of his illness); apparent mental retardation; moderate contracture right lower extremity	In orthopedic hospital

ture was 101.0° F., her pulse was 110 per minute and her respirations were 22 per minute. The cerebrospinal fluid contained 388 cells per cubic millimeter, lymphocytes predominating, 102 mg. total protein per 100 ml., and heavy reaction for globulin. She was given 20 c.c. of gamma globulin on admission and another 20 c.c. twenty-one hours later (a total dosage of 0.6 c.c. of gamma globulin per pound of body weight). Thirty-one hours after admission her temperature was 99.4° F., pulse 90 per minute, and respirations 24 per minute. Thirty-six hours after admission she was out of coma. Ten days after admission she still had moderate right facial paralysis, dilated pupils, bilateral papilledema, and hyperactive reflexes.

What effect does the administration of gamma globulin without antibiotics or sulfa drugs have on the course of the illness? Four patients, 27, 37, 38 and 40, received gamma globulin but no antibiotics or sulfa drugs in the acute stage of the illness with the same rapid clinical improvement as those patients who received gamma globulin together with antibiotics and sulfa drugs. Pneumonia did not develop in any of these patients. Case 38, while given only gamma globulin and showing excellent improvement as evidenced by her coming out of coma thirty-six hours after admission, suddenly developed an elevated temperature (105.6° F.) sixty-four hours after admission (Fig. 1). This was attributed to a cellulitis of the right thigh which occurred at the site of the insertion of the needle from a clysis. The cellulitis cleared up rapidly when antibiotics were given. From this it may be inferred that gamma globulin does not have the bactericidal properties of antibiotics. Conversely when antibiotics were given alone as in Group I (Table II) or in conjunctions with small doses of gamma globulin as in Group II (Table III) the results were not so good as in those cases where gamma globulin in doses large enough to confer a state of passive immunity were administered as in Group III (Table IV). Therefore, we have concluded that suitable doses of antibiotics and sulfa drugs must be given for the prophylaxis of secondary infection while the patient is critically ill, but it is the gamma globulin that effects the rapid clinical improvement in measles encephalitis and encephalomyelitis.

The gamma globulin should be administered in adequate doses and at frequent intervals depending on the clinical picture and for a period of time sufficient for the danger of relapse to have passed. One very large dose may not be enough. It is necessary to maintain a concentration of antibodies that is always greater than the concentration of viruses, that is, an amount of antibodies sufficient to neutralize the viruses in the acute phase. The concentration of a single dose of injected antibodies decreases very rapidly. This was shown experimentally by Bodian[32] who injected gamma globulin intramuscularly into monkeys. (We are referring to the work on the antibodies of the viruses of poliomyelitis since no comparable work has been done on measles antibodies.) Bodian found that a single dose of 0.92 ml. per pound had its highest concentration one day after injection and was just detectable in the serum three weeks later. A single dose of 4.6 ml. per pound had its highest concentration one day after injection and was just detectable six weeks later. Bodian estimated that the half-life of the

passive antibody for the Lansing strain of poliomyelitis virus was eight days. However, no determination of the persistence of antibodies in cerebrospinal fluids of either human beings or monkeys, or of the persistence of antibodies in sera of critically ill patients has been made and, therefore, the total dosage of gamma globulin to be given to these critically ill patients has to be determined empirically.

That single doses of gamma globulin or doses given at sporadic intervals are not efficacious in measles encephalitis and encephalomyelitis is illustrated by several of our case histories as follows:

CASE 39.—A 5-year-old child came in with a history of onset of measles rash three days before admission. Four hours prior to admission she fell out of her crib, struck her back on a nearby chair and landed on her head. Three hours later she complained of blurred vision, vomited, became stuporous, and was brought to the hospital. Her cerebrospinal fluid revealed 33 cells per cubic millimeter, lymphocytes predominating, 45 mg. total protein per 100 ml., and 2.0 mg. inorganic phosphorus per 100 ml. Because of the history of a fall, a skull fracture was considered; however, because of the measles rash and abnormal cerebrospinal fluid findings a diagnosis of encephalitis was entertained and 20 c.c. of gamma globulin was given on admission (a dose of 0.49 c.c. per pound of body weight). She was placed in oxygen and appropriate adjunctive therapy was instituted. Within thirty-six hours the temperature dropped from 104.8° F. on admission to 99.6° F.; she was alert, completely oriented, and clinically improved. Because of her very rapid recovery there was the possibility that we were dealing with a contusion or concussion of the brain rather than an encephalitis and the gamma globulin was discontinued. Two days later she had convulsions, her temperature rose to 106.8° F., and she was transferred to another hospital for possible neurosurgery. Three days later, since neurosurgery was not indicated, she was transferred back to our hospital. On the second admission she was not responsive and had a vacant stare although she was not stuporous. The pupils were dilated. Her mouth was open and her tongue protruded. Her temperature was 99.0° F. The cerebrospinal fluid inorganic phosphorus now was 4.1 mg. per 100 ml. (see second paper) indicating extensive destruction of nervous tissue. She was given 10 c.c. of gamma globulin. (Note normal temperature at this time in Fig. 1). This dose given a week after the first dose had no apparent effect on her subsequent clinical course since she made a slow recovery which would probably have ensued without this 10 c.c. dose.

CASE 28.—This 5½-year-old child was admitted to the hospital four days after the onset of the measles rash. On admission he was convulsing vigorously and his pupils were dilated and fixed. Afterward he lapsed into coma. His temperature was 108+° F. (compare the course of this patient with Case 23 in Table III who had the same degree of hyperthermia but who was given only a total dosage of 0.10 c.c. of gamma globulin per pound of body weight), his pulse was 148 per minute, and his respirations were 40 per minute. The cerebrospinal fluid revealed 78 cells per cubic millimeter, mostly lymphocytes, and a total protein of 110 mg. per 100 ml. He received 20 c.c. of gamma globulin, the only dose during his hospitalization (a total dosage of 0.44 c.c. of gamma globulin per pound of body weight), and suitable adjunctive therapy including antipyretic therapy. Twenty-four hours later his temperature dropped to 101.0° F. and he began to moan and move his left arm. Within the following thirty-six hours his

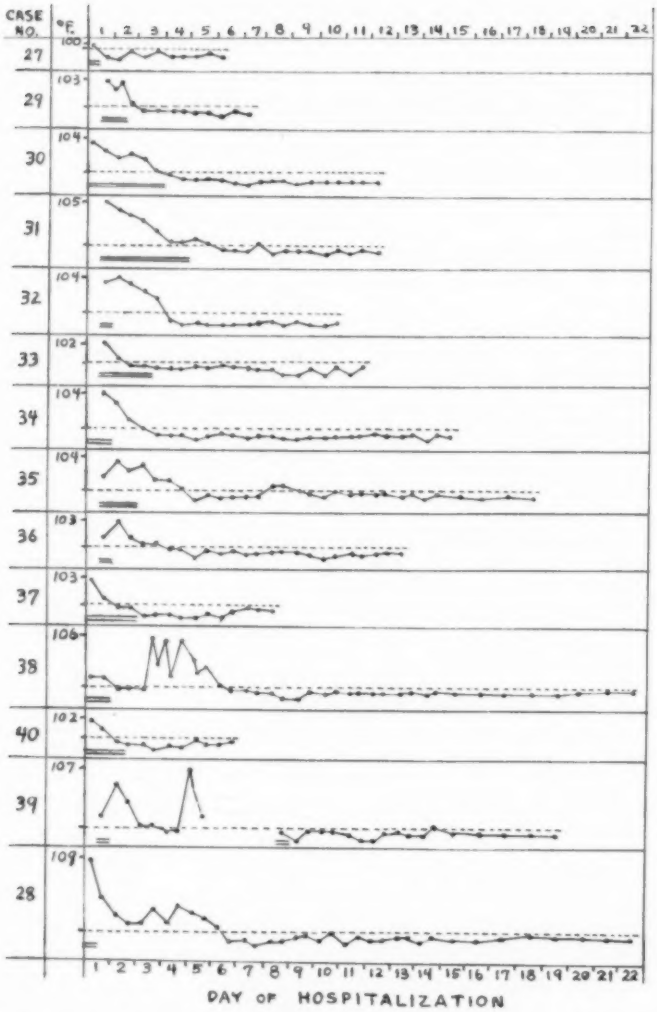

Fig. 1.—Temperature charts of patients who received 20 c.c. or more of gamma globulin—Group III. The broken line represents the normal temperature rectally. The double line underneath each temperature curve indicates the period during which gamma globulin was administered. Note that in every case there is a rapid temperature drop which is not uniformly encountered in patients not treated with gamma globulin. Cases 27, 37, 38, and 40 received only gamma globulin (no antibiotics or sulfa drugs) in the acute phase with the same rapid drop in temperature as the other cases. The sharp spike to 105.6° F. in Case 38 was due to a cellulitis of the thigh; antibiotics were started at this point with the result that the cellulitis subsided and the temperature dropped to normal. Case 39 received only a single dose of gamma globulin on admission. The second spike in the temperature curve is attributed to a relapse or a recrudescence. The gap in the temperature curve occurred during the interval when the child was at another hospital for possible neurosurgery because of the complicating history of a head injury. Case 28 with an admission temperature of over 108° F. received only a single dose of gamma globulin. Note that his temperature took the longest to come down to normal. He was the only one in Group III left with severe residuals.

temperature rose sharply to 103.8° F. and then took 3 days to drop to 98.6° F., the pulse and respirations paralleling the temperature. At this time he had a right-sided hemiplegia and right facial paralysis. He was coming out of coma. He made a steady but slow recovery and was transferred to an orthopedic hospital with a right hemiparesis, right facial weakness, and speech difficulty after a hospital residence of fifty-five days.

Cases 28 and 27 received the lowest doses of gamma globulin in Group III, total dosages of 0.44 and 0.43 c.c. of gamma globulin per pound of body weight, respectively. Case 28 came in with an initial temperature so high that it was never precisely determined and therapy was promptly started while the temperature of Case 27 had dropped to 99.8° F. on admission from a preadmission temperature of 104.0° F. The condition on admission of Case 28 was much worse than that of Case 27.

Case 41.—Our most critical case received the largest dose of gamma globulin. For four weeks it was the opinion of all the physicians including the consultants who saw this child that his prognosis was grave.

First Week. This 7-year-old child was admitted in stupor to the hospital on May 15, 1952, at 7:00 P.M. with a five-day history of measles. Two days prior to admission he refused food and fluids. Somnolence, lethargy, and loss of sphincter control of the urinary bladder followed shortly thereafter. On admission the temperature was 99.0° F., the pulse 60 per minute, and respirations 20 per minute. During the physical examination he kept opening his eyes, looking about, whining, and drifting back into lethargy. His pupils were widely dilated and did not react to light or accommodation. The fundi showed papilledema. There was nystagmus. The deep reflexes were hyperactive. The abdominal and cremasteric reflexes were absent. He was given 20 c.c. of gamma globulin, placed in an oxygen tent, and a clysis started. Some hours later he appeared more alert in that he responded to questions by nodding his head. On the following morning at 7:00 A.M. he was stuporous, spastic, and had tremors of the extremities. The temperature was 99.8° F., pulse 120 per minute, and respirations 40 per minute. At 11:00 A.M. 20 c.c. of gamma globulin was given. Ten milligrams of Priscoline was administered and was repeated every two hours. One and one-half hours later his condition became worse. He was comatose and his respirations became rapid and shallow. During that afternoon and evening he failed to respond to painful stimuli as injections. He was given fluids and sedatives for the convulsive tremors. On May 17 his temperature was 101.0° F., pulse 180 per minute, and respirations 50 per minute. The physical examination disclosed pulmonary edema and fluids were therefore discontinued for eight hours. His condition remained precarious until the following morning when the Priscoline was discontinued at 9:00 A.M. At this time his temperature was 101.4° F., pulse 170 per minute, and respirations 42 per minute. At 11:00 A.M. another 20 c.c. dose of gamma globulin was given. On May 18 his temperature went down to 98.0° F., pulse to 130 per minute and respirations to 32 per minute. During the remainder of the first week he was given 26 c.c. of gamma globulin but his condition remained critical; it was noted that the patient reacted only to painful stimuli.

Second to Fifth Weeks. He remained stuporous and whined frequently. There was marked pallor of the optic discs; the nerve heads appeared atrophic. The swallowing reflex was absent. His upper extremities were spastic and flexed and exhibited fine tremors; the lower extremities were flaccid but responded slightly to painful stimuli. The temperature during the second week was normal except for one rise to 101.0°

F., but the pulse and respirations were erratic. At the beginning of the third week his temperature suddenly rose to 103.8° F. (Fig. 2) and then fluctuated between 99.6° F. and 105.6° F. This was interpreted as indicating involvement of the hypothalamus or a relapse caused by a reincubation of the virus. Because of the latter possibility gamma globulin was continued; 130 c.c. was given during this period. The pulse and respirations continued erratic, rising to 160 and 44 per minute, respectively. The patient maintained his admission weight and was well nourished on gavage feedings.

Sixth to Tenth Weeks. The patient made slow and progressive improvement during this period. He became alert and oriented. His speech, not intelligible at first, gradually became more comprehensible. He regained his vision. He started to accept fluids by medicine dropper. Muscle strength and motion improved in all extremities. His legs were painful, more so to pressure than to touch. The abdominal reflexes were elicited. He was incontinent of urine and feces. The temperature, pulse, and respirations came down to lower levels, reaching peaks of 102.4° F., 120 and 32 per minute, respectively. He was slowly weaned away from the oxygen tent.

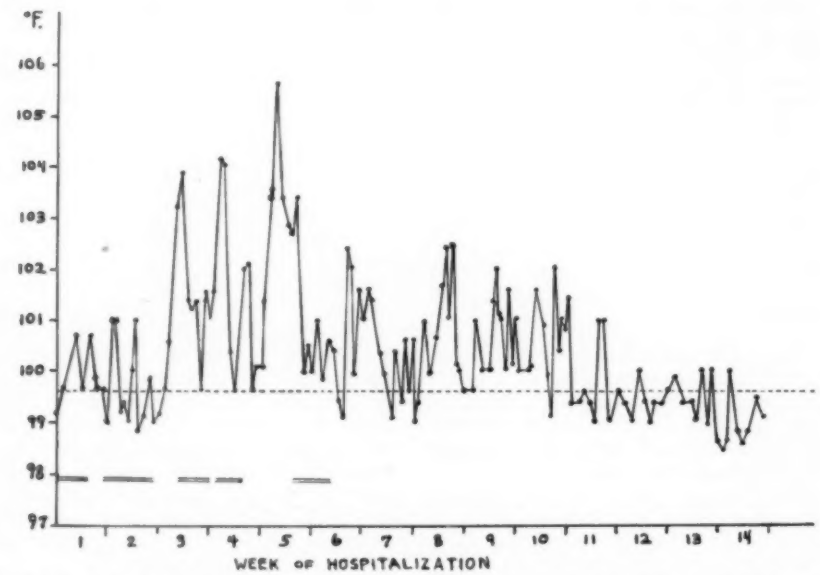

Fig. 2.—Case 41. This patient was the most critically ill of Group III and one of the most desperately ill of the entire series. The broken line represents the normal temperature rectally. The double line underneath the temperature curve indicates the period during which gamma globulin was administered. Case 41 received the largest amount of gamma globulin of the series. The spikes in temperature commencing in the third week were thought to be due to reincubation of the virus or damage to the temperature control mechanism of the brain or both. The patient made a moderately good recovery.

Before we sum up the patient's status on discharge a brief note on his past history is in order. The patient was abandoned by his parents and is being reared by his aunt and uncle. His aunt stated that the patient was always shy and introverted. She added that he was not completely toilet trained for urine or feces at the time of his illness (at the age of 7 years).

Six months after admission the patient was transferred to an orthopedic hospital. At the time of transfer he drooled frequently; his vision was good; he spoke slowly and coherently; and he appeared mentally retarded. There was some facial masking. He was incontinent of urine and feces. All the extremities were normal except for the right lower in which there was a moderate contracture of the hamstring muscles. His aunt said that the patient's mental status was not altered from that prior to his encephalomyelitis.

That large doses of gamma globulin have little demonstrable effect in the recovery phase is illustrated by the following patient who received 45 c.c. of gamma globulin seventeen to twenty-one days after admission.

CASE 1.—This 10-year-old child was admitted to the hospital six days after the appearance of the measles rash. On admission he was drowsy and he had difficulty with his speech. There was diplopia, lack of convergence, and sluggish pupillary reflexes. The abdominal reflexes were absent and the deep tendon reflexes were hypoactive. The cerebrospinal fluid findings were: 340 cells per cubic millimeter, polymorphonuclear leukocytes predominating, and 132 mg. total protein per 100 ml. The patient spiked a temperature that reached 106.4° F. in twenty-four hours and at the same time he lapsed into coma. On the fourth day after admission he began to come out of coma and by the sixth day he was rational and responded to questions. However, the temperature continued

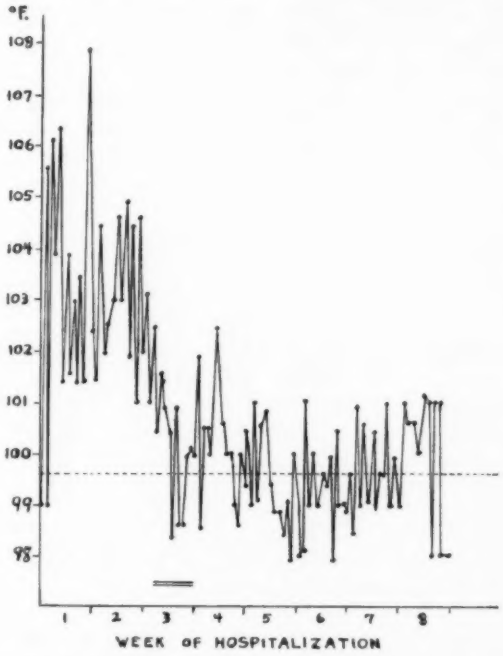

Fig. 3.—Case 1. The broken line represents the normal temperature rectally. The double line underneath the temperature curve indicates the period during which gamma globulin was administered. This patient received 45 c.c. of gamma globulin from the seventeenth to the twenty-first days of hospitalization. The temperature dropped to the normal level for the first time after gamma globulin was given.

to spike between 101.0° F. and 104.6° F. (Fig. 3). Seventeen days after admission gamma globulin was given. The neurological findings at this time were left facial weakness, weakness of all extremities which was more marked on the right side, and absent abdominal and cremasteric reflexes. Forty-five cubic centimeters of gamma globulin was given over a five-day period and for the first time the temperature dropped to 98.6° F. rectally (Fig. 3). Thirty-six hours after the gamma globulin was discontinued the temperature began to spike again to 102.4° F. until two days prior to discharge (Fig. 3). At the time of discharge there was moderate weakness of the arms and legs with spasticity, hyperactive knee jerks, and ankle clonus.

the treatment of measles encephalitis and encephalomyelitis.

There was no mortality, a greatly reduced incidence of sequelae, and a reduction in the severity of sequelae in Group III (who received a total dosage of 0.43 to 1.1 c.c. of gamma globulin per pound of body weight in the acute phase) as compared with Group I (no gamma globulin in the acute phase) and Group II (who received a total dosage of from 0.07 to 0.30 c.c. of gamma globulin per pound of body weight in the acute phase) and the cases reported in the literature (Table I). Notable also was the absence of pneumonia in the

TABLE V. GAMMA GLOBULIN IN MEASLES ENCEPHALITIS AND ENCEPHALOMYELITIS; COMPARATIVE RESULTS OF THREE GROUPS OF PATIENTS

GROUP	TOTAL DOSE OF GAMMA GLOBULIN C.C.	NUMBER OF CASES	CLINICAL PICTURE ON ADMISSION		RESULTS			
			SEVERE PER CENT	MODERATE PER CENT	DIED PER CENT	SEVERE RESIDUALS PER CENT	MODERATE OR MINIMAL RESIDUALS PER CENT	COMPLETE RECOVERY PER CENT
I (Table II)	None	14	57	43	14*	7	36	43
II (Table III)	4-16	12†	67	33	25	0	25	50
III (Table IV)	20	15	80	20	0	7	33	60

*One patient died during a convulsion after discharge.
†Case 16 is included in this group because this patient received 10 c.c. of gamma globulin; however, she also received 250 c.c. of whole blood and 550 c.c. of plasma which is equivalent to a total of approximately 35 c.c. of gamma globulin. She made a complete recovery. By including Case 16 with Group III the complete recovery rate is increased to 63 per cent.

Although the administration of 45 c.c. of gamma globulin on the seventeenth, eighteenth, nineteenth, twentieth, and twenty-first days of hospitalization produced a drop in temperature temporarily, it was not considered that the gamma globulin given so late after the onset of the encephalitis altered the clinical course appreciably.

EVALUATION OF GAMMA GLOBULIN THERAPY

A detailed analysis of our cases shows that successive large doses of gamma globulin were efficacious in series of patients who received therapeutic doses of gamma globulin. There were gratifying reductions in the incidence of other secondary complications and in the length of hospital stay (compare Tables II and III with Table IV). In many cases with extensive severe central nervous system involvement the neurological symptoms were resolved very rapidly and the temperature (Fig. 1), the pulse, and the respirations quickly came down to normal and stayed there.

The complete recovery rate—the percentage of patients who recovered without any apparent residuals—was highest in Group III though this group had the greatest number of desperately ill patients (Table V).

Many of our patients were examined after they had returned to school. Except where noted in Tables II, III, and IV no problems were encountered either at home or at school.

The series of sixteen patients treated with large doses of gamma globulin (fifteen patients from Group III and Case 16 from Group II) who had been critically ill with measles encephalitis or encephalomyelitis without a single death is without precedent in medical literature although two series with a low mortality rate have been reported: Roos[26] (6 per cent of eighteen patients) and Spragins, Shinners, and Rochester[31] (6 per cent of thirty-one patients). The fact that blood substances including serum and placental gamma globulin have been used in many of the series of cases in Table I makes it impossible to appraise the true value of gamma globulin from the cases reported in the literature.

Kingston Avenue Hospital is the Communicable Disease Hospital for the nearly 3 million people of Brooklyn, New York City. Four of us (K. G. J., I. J. S., H. W., and B. N.), who have been associated with this hospital for twenty-five years or longer and have had the opportunity to observe a few hundred measles cases with central nervous system complications, concluded from our experience that therapy with gamma globulin is a very effective method of treatment. Moreover, when our cases are compared with the cases of a previous publication from this hospital (Litvak, Sands, and Gibel[27]) of fifty-six carefully detailed cases of measles encephalitis with follow-up studies in thirty-two, when no gamma globulin was used, the outcome of our present series, Group III, is striking.

We believe that therapy with large, successive doses of gamma globulin at the onset of encephalitis or encephalomyelitis in measles reduced the mortality rate, the incidence of sequelae, and the severity of sequelae, and that the comparison of our three groups of cases has substantiated this opinion.

REACTIONS TO LARGE DOSES OF GAMMA GLOBULIN

All the gamma globulin was injected intramuscularly into the buttocks.

There were no local or systemic reactions to the gamma globulin injections.

The patients who received gamma globulin were followed for a period of time varying from one month to two years. Nineteen patients were followed for four or more months (Tables III and IV). No reactions were reported by the parents of the children or the private physicians of these patients.

RECOMMENDED DOSAGE OF GAMMA GLOBULIN FOR MEASLES ENCEPHALITIS AND MEASLES ENCEPHALOMYELITIS FOR CHILDREN UNDER 14 YEARS OF AGE

Based on the analysis of the data in our cases we recommend a total dosage equivalent to 1 c.c. per pound of body weight except that not less than a total of 30 c.c. be given to any very

young child because of the increased metabolic rate. If the temperature rises above 103° F. (rectal) we advise that an additional 10 c.c. be added to the total dosage for children 6 years of age or younger and that 20 c.c. be added to the total dosage for children over 6 years of age.

In order to give the patient the greatest advantage of gamma globulin therapy, the injections should be started as soon as the signs and symptoms of central nervous system involvement are manifest.

The total dosage should be given within a period of thirty-six to forty-eight hours.

Suggested schedules for administering the total dosage are illustrated by the following examples:

(a) *Total dosage of 50 c.c.*
20 c.c. on admission
20 c.c. 12 hours later
10 c.c. 24 hours after the second injection

(b) *Total dosage of 80 c.c.*
30 c.c. on admission
20 c.c. 12 hours later
10 c.c. 12 hours after the second injection
10 c.c. 12 hours after the third injection
10 c.c. 12 hours after the fourth injection

We would like to emphasize that acquired immunity is the desired condition and that passive immunity conferred by therapeutic doses of gamma globulin should be reserved only for those critical cases where the effects of the virus would produce serious consequences.

The administration of high doses of gamma globulin in dehydrated patients may cause a shift in osmotic pressure with subsequent elevation in temperature.

Therefore, if the patient is dehydrated, plasma and fluids by vein, clysis, and mouth should all be started first, before gamma globulin is given. Then gamma globulin should be administered in smaller doses and at more frequent intervals than in the schedules suggested above and the fluid intake and output should be carefully observed. Since 100 c.c. of plasma is equivalent to about 4 c.c. of gamma globulin, the equivalent amount of gamma globulin may be subtracted from the total dose.

Gamma globulin is of limited supply and its use should be restricted to those diseases and infections for which no other therapy is available. The memory of the truly crippling sequelae and psychoses resulting from measles encephalitis and encephalomyelitis in years past when no gamma globulin therapy was employed leaves no doubt that this blood concentrate should be administered to patients critically ill with these central nervous system complications of measles.

ADJUNCTIVE THERAPY

Adjunctive therapy is as important as gamma globulin.

The gamma globulin neutralizes the virus while the adjunctive therapy is essential to sustain the patient physically in the acute stage and to realize a more rapid and complete recovery.

We feel that much of the effectiveness of gamma globulin will be nullified if the patient's excessive fever is not promptly reduced, if his dehydration is not promptly corrected, if his catabolic processes proceed at a rate far exceeding his anabolic processes, i.e., if he is starving and remains unfed, if his convulsions and

restlessness are not reduced by judicious sedation, if his anoxia is not remedied by oxygen, if he is unable to swallow or he is comatose and his secretions are not removed by frequent suctioning.

The following measures were instituted and varied according to the clinical condition of the patient.

1. *Anticonvulsive Therapy.*—In most cases convulsions were effectually controlled by the intravenous or the intramuscular administration of one of the barbiturates (sodium phenobarbital or Sodium Amytal). In more resistant cases supplementary sedation was provided by the rectal instillation of chloral hydrate in water. If convulsions still persisted, they were checked by the administration of ether by mask. We were rather reluctant to resort to the last method, however, because of the danger of increasing intracranial pressure.[33]

For restlessness small doses of sedatives were employed.

2. *Antipyretic Therapy.*—Nearly all our cases manifested hyperpyrexia. The usual measures for reducing fever such as alcohol sponges, cold sponges, colonic flushes, and acetylsalicylic acid were applied promptly.

3. *Spinal Puncture.*—Spinal punctures were performed only for diagnostic purposes and never for therapeutic reasons.

4. *Oxygen.*—All patients who were in coma or who were stuporous were placed in oxygen tents and kept there until fully conscious and their hypoxia was rectified. This procedure was employed in an attempt to maintain a normal respiratory gas exchange in our patients. Increasing the arterial oxygen concentration alone is not sufficient to rid the CO_2 that has been accumulated in patients with depressed, shallow, and irregular respirations with possible extensive damage to the respiratory center of the brain. To wash out the CO_2 adequate ventilation is also necessary. In instances such as these Motley[34] recommended the use of "intermittent positive pressure breathing" in order to furnish a more uniform aeration of the alveoli which are poorly oxygenated but still perfused with blood. Intermittent positive pressure breathing will minimize the accumulation of bronchial secretions and preclude atelectasis. In general oxygen therapy as outlined above will help support the metabolism of severely injured tissues from the possibility of continued hypoxia provided all other requisite factors for the utilization of oxygen in the brain are present.

5. *Fluids.*—Most of the patients who are admitted as measles encephalitis or encephalomyelitis have or have had episodes of vomiting, continuous fever, convulsions, or are in coma. Very probably their fluid intake during the previous days had been inadequate. The correction of their fluid and electrolyte balance is therefore of the utmost importance. If the patient could swallow, all fluids were given by mouth, otherwise fluids were administered by the parenteral route and by gavage; hypodermoclysis was preferred over the intravenous method in order to avoid the possibility of pulmonary edema. The usual repair solutions such as glucose, glucose in physiologic saline, or Ringer's lactate were employed depending upon clinical and laboratory indications. Al-

though it appears paradoxical to institute dehydration measures in already dehydrated patients, attempts were made to reduce "cerebral edema" by the use of hypertonic dextrose solutions, intramuscular magnesium sulfate, and caffeine and sodium benzoate, none of which produced any measurable improvement in the patient's condition in the few cases where they were used. Indeed the cerebral edema occasionally observed in pathologic studies of measles encephalitis and encephalomyelitis might be due to a necessary attempt on the part of the central nervous system to maintain the osmotic pressure at as normal values as possible under the condition of greatly increased quantities of protein and other debris resulting from the breakdown of tissue. Thus, adequate fluid intake is of paramount importance in the treatment of these infections.

6. *Nutrition.*—In the past insufficient recognition was given to the fact that in measles encephalitis and encephalomyelitis, children with high fever and a dehydrating process are undergoing severe tissue destruction and therefore their nutritional state should be adjusted promptly. For this reason gavage feedings were instituted immediately on admission consisting of a high caloric liquid diet rich in proteins, carbohydrates, vitamins, and minerals (electrolytes), and in addition high in lipids, cholesterol, and phosphorus together with small doses of magnesium in the form of milk of magnesia or small doses of magnesium sulfate intramuscularly. These feedings were alternated with water and fruit juices. Strained baby foods, such as fruits, vegetables, and meat (including liver) and mashed bananas, all diluted with water, were easily given by gavage. In no patients were there any ill effects or gastrointestinal upsets noted. Regurgitation and aspiration of fluids were avoided by careful feeding in small amounts. When the patients came out of coma or became able to swallow, an especially enriched diet was given which was high in vitamins, minerals (including milk which provides an ample quantity of phosphorus), and was supplemented by eggs, ice cream, and egg custards which are excellent sources of cholesterol.

An adequate supply of metabolites is essential during the period when catabolism is reverting to normal metabolism and when destroyed central nervous system tissue is being repaired.

The role of the metabolites phosphorus, cholesterol, and magnesium, substances which are not usually considered in measles encephalitis and encephalomyelitis, will be discussed in a second paper. Our serum and cerebrospinal fluid studies in these patients revealed interesting data on phosphorus and cholesterol.

7. *Suction.*—Suction is necessary where there is increased secretion of mucus concurrently with an inability to swallow. It should be done frequently and gently to minimize irritation to the mucous membranes, reduce the secretion of mucus, and prevent aspiration.

8. *Care of the Bowels.*—In patients with intestinal atony frequent enemas were employed. In stubborn cases Harris irrigations or oil retention enemas brought good results. A few patients had to be disimpacted manu-

ally. Prostigmine was used in one case without success.

9. *Care of the Bladder.*—Urinary retention was relieved by catheterization every eight hours until bladder control was established. Stubborn cases were treated with tidal drainage. Furmethide was used in two cases with excellent results and without any side effects.

10. *Medication.* — Gamma globulin, magnesium in small doses, antibiotics and sulfa drugs, barbiturates if needed, and oxygen as needed comprise the list of effective medication in measles encephalitis and encephalomyelitis.

We have used Priscoline in four cases. In every instance there was an increase in the pulse rate, the increase varying from 14 to 30 beats per minute depending on the size of the dose. In Case 41 (discussed above) Priscoline had a deleterious action. Cases 22, 36, and 38 received Priscoline in the recovery phase with tachycardia, nausea, and vomiting, whereupon Priscoline was discontinued with cessation of the side effects. Priscoline is seemingly contraindicated in measles encephalitis and encephalomyelitis.

Adrenal cortical hormone derivatives were given to eight patients (Cases 16, 22, 23, 28, 32, 34, 35, and 38; see Tables III and IV). In each instance we have noted the total dose and the number of days over which the hormonal derivative was administered. All these cases were severe—desperately sick children. No definite conclusion can be drawn from our cases that adrenal cortical hormone derivatives influenced for better or worse the course of measles encephalitis or encephalomyelitis.

11. *Paresis, Paralysis, or Spasticity of Extremities.*—Where there was paresis, paralysis, or spasticity, appropriate physiotherapy measures were instituted.

COMMENT

We believe that our results show that gamma globulin administered in the acute stage and in sufficient therapeutic doses, together with proper adjunctive therapy, is effective in reducing the mortality rate, and the incidence and the severity of sequelae from measles encephalitis and encephalomyelitis. Further, it is probable that similar results can be achieved with therapeutic doses of gamma globulin in viral infections and with complications of the central nervous system other than measles, although for maximum efficiency it might be necessary to titer each lot of gamma globulin, if possible, or to prepare gamma globulin for the various infections from convalescing patients. The administration of gamma globulin by the intrathecal route simultaneous with intramuscular injections should be investigated.

The dictum that serum therapy in any form is valueless for the treatment of the complications of measles is no longer tenable in the light of the recoveries of our critically ill patients who received therapeutic doses of gamma globulin and proper adjunctive therapy as soon as the signs and symptoms of central nervous system involvement were manifest.

SUMMARY AND CONCLUSIONS

Forty-one cases of measles encephalitis and encephalomyelitis with fol-

low-up studies have been presented in detail; fifteen patients received 20 c.c. or more of gamma globulin early in the acute phase (a total dosage of from 0.43 to 1.1 c.c. of gamma globulin per pound of body weight); twelve patients received from 4 to 16 c.c. of gamma globulin early in the acute phase (a total dosage of from 0.07 to 0.30 c.c. of gamma globulin per pound of body weight); and fourteen patients were not treated with gamma globulin in the acute phase.

The results in the group given 20 c.c. or more (a total dosage of 0.43 c.c. or more per pound of body weight) were better in every respect than those of the other two groups. This group had a greater apparent complete recovery rate, a reduced incidence in the severity of sequelae, a normal temperature by the third day (mean of fourteen out of fifteen cases), a shorter hospital residence, no fatalities, and no secondary complicating pneumonia. The patients made remarkable recoveries in view of their signs and symptoms betokening extensive nervous system involvement. Four patients received gamma globulin alone (no antibiotics or sulfa drugs) in the acute phase and made the same rapid recovery as those given antibiotics or sulfa drugs in combination with the gamma globulin injections.

There were no local or systemic reactions to therapeutic doses of gamma globulin.

The recommended dose is a total dosage of 1 c.c. per pound of body weight, given intramuscularly in divided doses, over a thirty-six- to forty-eight-hour period, as soon as the signs and symptoms of central nervous system involvement are manifest. Suggested dosage schedules are given.

Gamma globulin therapy can be expected to shorten the acute stage of measles encephalitis and encephalomyelitis and as a result (1) reduce the incidence of sequelae, (2) reduce the severity of sequelae, and (3) reduce the mortality rate. It may not be possible to see every patient recover without sequelae inasmuch as neurological signs indicative of central nervous system tissue destruction subsequent to viral invasion are already present when treatment with gamma globulin is commenced.

Gamma globulin is of limited supply and its use, therefore, should be restricted to those infections for which no other treatment is available.

Adjunctive therapy is mandatory to assure the fullest recovery to the patient. The therapeutic regime in measles encephalitis and encephalomyelitis includes in addition to gamma globulin, adequate fluid and electrolyte intake, oxygen, antipyretic therapy, suction, balanced nutritional feedings, sedatives (barbiturates) in small doses as needed, magnesium sulfate in small doses, antibiotics, and sulfa drugs.

Several new hypotheses to explain the occurrence of measles encephalitis and encephalomyelitis in only a very small percentage of cases based on a virus-antibody relationship in a human host, are suggested. The rationale of gamma globulin therapy rests tentatively upon these hypotheses.

We suggest that gamma globulin and adjunctive therapy can be used in the treatment of viral complications of the central nervous system other than measles with good results.

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MESENTERIC OCCLUSION IN A NEWBORN INFANT

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OCCLUSION of the superior mesenteric artery is very rarely encountered in infants and children. We wish to describe our experience with such a lesion in a newborn infant.

A number of cases of mesenteric vascular occlusions have been reported in adults. According to Rives and associates,[1] they occur in about one or two out of 1,000 surgical admissions; most often they are encountered in the third to sixth decade. These authors reported nineteen cases from 1939 to 1947. Their youngest patient was 26 years of age. Strohl and Lassner[2] found that 900 cases had been reported up to 1950. Musgrove and Seybold[3] state there were twenty-four cases at the Mayo Clinic from 1938 through 1948. Their youngest patient was 35 years old.

In Trotter's[4] series of 366 cases, only four were beween the ages of 1 and 10 years. Johnson[5] reported the lesion in an infant at 6 weeks. Frank[6] reported its occurrence in three children; Feldstein and Goldstein[7] found it in a 6-year-old girl. Gross,[8] in his tabulation of cases of arterial embolism and thrombosis in infancy from 1900 to 1945, mentions only three examples of mesenteric thrombosis.

CASE HISTORY

A male infant was born at term on Dec. 4, 1952, by breech. He weighed 5 pounds 7 ounces. The mother was 23 years of age and had had two previous abortions. She is Rh negative and the husband Rh positive. There were no antibodies or agglutinins demonstrated in her blood a week before the delivery. Cord blood was Rh negative, type A.

For the first twelve hours of life the infant's condition seemed precarious. His temperature was subnormal; he was cyanotic and muscular tone was poor. Gallop rhythm was noted and some degree of cardiac enlargement was thought to exist. He was kept in an incubator and oxygen was administered.

On the second day he seemed to have improved. His color was better. He took nine ounces of a solution of lactose in water. There was no vomiting and a normal meconium stool was passed.

On the third day of life he seemed to be progressing well. He took 9 ounces of lactose water, had two normal stools and one loose, green movement. On the fourth day he looked well enough to be taken out of oxygen and he consumed 11 ounces of a diluted milk formula. He was perhaps a little icteric.

On the fifth day the clinical picture changed. He vomited once and had a normal stool. Because of progressive jaundice, lassitude, and lack of any positive, localized physical findings, the infant was thought to have septicemia, although no fever was present at any time. Antibiotics and clyses of 5 per cent glucose in distilled water were given. He took formula well but the clinical picture was that of a sick, icteric infant.

Weight loss was not excessive—6 ounces in five days, relieved by clyses on the sixth day.

Late on the sixth day he passed one normal stool which contained small milk curds, and then one loose stool

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containing blood. He looked more ill. Then, because of the first vomiting attack in which the presence of bile was noted, intestinal obstruction was considered. The only abnormal finding about the abdomen was distention. No masses could be felt; no spasm was detected; no peristalsis was seen or heard; and bowel sounds seemed normal.

Fluoroscopic examination, together with roentgenograms of the abdomen in erect and supine positions, revealed moderate gaseous distention of the stomach, with a fluid level. In addition, there was intestinal distention, apparently principally involving the large bowel. Some gas within the pelvis was apparently in the rectum.

Fig. 1.—Photomicrograph showing superior mesenteric artery occluded by partially organized thrombus.

A hemogram on the second day showed that there were 7 million red blood cells per cubic millimeter. The hemoglobin level was 21.4 grams. There were 28,200 leukocytes per cubic millimeter; 64 per cent neutrophils and 36 per cent lymphocytes, and six nucleated red blood cells per 100 white blood cells. A repeat count taken on the third day showed a drop to 5.6 million red blood cells; 18.6 grams of hemoglobin; 10,200 white blood cells. No nucleated red blood cells were noted. The bleeding time was 2 minutes; the coagulation time was 3 minutes 20 seconds. Blood cultures taken on the fourth day were negative.

The heart and lungs appeared to be normal. A swallow of Lipiodol was given. The esophagus and stomach appeared normal. The descending duodenum was dilated. The dilatation appeared to be on the basis of an obstruction visualized in the midportion of the transverse duodenum. The superior margin was indented, only a thin column of Lipiodol being seen to pass this point inferiorly. The distal duodenum was dilated as was the jejunum immediately beyond the ligament of Treitz. An area of narrowing appeared to be present in the jejunum, a loop presenting a narrowed

portion which seemed to be in fair proximity to the transverse duodenum.

Interval studies then indicated slow progress of Lipiodol through the proximal small bowel, the opaque medium at 3 hours being in the midportion. It appeared to be about 5 to 6 inches proximal to what was believed to be an obstruction. Some gas was observed in the distal colon in interval films. From these studies we believed there were multiple areas of partial obstruction in the small bowel, probably due to adhesions in the mid-transverse duodenum, proximal jejunum and ileum. The roentgen findings, as described by Harrington[9] and said to be most suggestive of mesenteric thrombosis, were not demonstrated.

At operation the peritoneal cavity contained considerable greenish fluid. Most of the small bowel was gangrenous, the color varying from yellow to purplish black, with scattered areas of plastic exudate. There was no peristalsis in the involved portion of the small bowel, nor were there any pulsations in the mesenteric vessels which supplied it. The duodenum, colon, and appendix were normal. The vasa recti in the mesocolon pulsated. No congenital abnormalities were noted. Palpation of the superior mesenteric artery revealed it to be thrombosed. The involved jejunum and ileum were resected and an end-to-end anastomosis was performed. The infant was returned to the ward in critical condition and he expired six hours later.

The specimen of small bowel removed at surgery measured 120 cm. in length, was dark bluish in color, congested and necrotic. There were segmental dilatations up to 1 cm. in diameter.

At autopsy the infant weighed 2,300 grams and measured 46 cm. in length. There were moderate jaundice and cyanosis of the lips and nail beds. Pertinent findings were limited to the gastrointestinal tract. There was 10 cm. of jejunum and 1.5 cm. of distal ileum remaining, the two connected by an intact suture line with a patent lumen.

Dissection of the vessels revealed a firm, pinkish, tight thrombus in the superior mesenteric artery 1.5 cm. in length, extending from just below the origin of the middle colic artery to the distal end of that vessel, which was tied with a cotton ligature; other vessels were normal. The ductus arteriosus was patent and there was no thrombus present.

Microscopic sections showed early organization of the thrombus in the superior mesenteric artery (Fig. 1).

COMMENT

In retrospect this patient had fairly typical clinical features of mesenteric vascular thrombosis. Several observations might have suggested this lesion preoperatively. First, the infant looked very ill before vomiting occurred; second, progressive and rather characteristic changes in intestinal symptomatology culminating in stools containing blood; and finally, distention. This slow development of intestinal obstruction after mesenteric vascular occlusion has been described many times in adults. Vomiting of bile-stained material occurred late. This made a presumptive diagnosis of intestinal obstruction almost mandatory. There are many cases of vascular mesenteric occlusion reported in adults, with technically extensive intestinal resections, but high mortality rates.

It would seem that the only hope for survival in an infant would be early recognition and embolectomy.

The etiological factor involved in our patient was not determined. As stated by Gross[8] and DeCamp and coworkers,[11] many thromboses occur in newborn infants, perhaps reflecting circulatory readjustments. No evidence of congenital heart disease was found. The ductus arteriosus did not contain a thrombus. Sepsis, trauma, or dehydration did not appear to be causative factors.

SUMMARY

An example of mesenteric arterial vascular occlusion in a newborn male infant is recorded.

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VARICELLA IN NEWBORN TWINS

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VARICELLA has been noted very rarely during the newborn period. Shuman[1] in 1939 found only five previously reported cases in addition to the one he recorded, and none has appeared since. The cases to be reported here were in twin girls who had chicken pox eruption at the time of birth and were admitted to the St. Louis Children's Hospital during the second week of life.

CASE REPORT

The twins were the first children of a 17-year-old white mother living in rural Missouri, who had been exposed to chicken pox two weeks previously and developed a typical vesicular eruption the day before delivery. Her eruption, which consisted of scattered vesicles over the trunk and extremities, lasted about a week and was considered to be typical mild varicella by her physician, Dr. B. A. Michaelis of Fredericktown, Mo. I am indebted to him for the observations on the infants previous to their hospital admission. The twin girls, born at home March 4, 1953, were fraternal and not identical.

Case 1.—Betty Sue weighed 2,400 grams (5¼ pounds) at birth and had fifteen to twenty small vesicles about the neck and face. While the vernix was being removed, several of these vesicles were ruptured and exuded a clear, colorless fluid. The physician had no doubt that the eruption was varicella. The mother stated that it had spread over the rest of the body during the first week of life. When the infant was seen at the age of 8 days, the rash was generalized and so extensive that she was referred to the hospital because the physician feared it was secondarily infected.

On admission on the eleventh day of life, an extensive eruption covered the trunk, face, scalp, and extremities, with a few lesions on the palms. The lesions were chiefly superficial vesicles, some with clear fluid and others slightly turbid. Some were umbilicated and others crusted, especially on the face. Between the vesicles the skin was somewhat reddened, with the appearance of an erythematous milia. A few small vesicles were present on the soft palate. There was no fever or evidence of secondary infection, and aspirated vesicle fluid was sterile. The remainder of the examination, including the blood and urine, was negative.

The lesions regressed slowly with crusting and desquamation, so that it was not until the twenty-fourth day of life (thirteen days after admission) that desquamation was complete, and she was discharged.

Case 2.—Mary Lou, the second twin, weighed 2,700 grams (6 pounds) at birth, and the presence of a vesicular eruption and its early course and appearance were essentially identical with that of her twin. She was admitted to the St. Louis Children's Hospital at 15 days of age because of diarrhea. On examination, the only difference in her eruption, which was vesicular and generalized, and that of Betty Sue was that the milial-like erythema between the vesicles was somewhat less marked. She was afebrile, and the moderately severe diarrhea slowly improved with fluid and antibiotic therapy. The eruption regressed and desquamated, so that by the twenty-fourth day of life there remained only a few scars.

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A few days later she again developed a severe diarrhea which persisted in spite of antibiotic and parenteral fluid therapy, and she died two weeks later. Necropsy showed ulceration of the duodenum and an extensive bronchopneumonia.

COMMENT

In summary, twin girls were born of a mother who developed a mild varicella eruption the day before delivery. Both twins had a few vesicles at birth which spread during the first week to produce a very extensive generalized chicken pox which persisted for at least two weeks longer before complete desquamation. The severity of the eruption and the long course were unusual. Many experienced observers who saw these infants shortly after admission were uncertain of the diagnosis of varicella but subsequently concurred. In the other reported cases, the lesions described were scattered and only in moderate numbers, of short duration, and similar to the eruption in older infants. There seems to be no reason to doubt that the lesions present at birth, in the twins described, were due to varicella and that the infection was transplacental.

In the other reported cases of varicella in the newborn infant, the time relationships between the disease in the mother and that in the infant has varied considerably. For example, in two instances in which the mother had varicella at the time of birth, the infant developed the disease at 8 days of age; in one, the mother's disease was two weeks before delivery, and the infant had the eruption at birth; in one, the mother's eruption was eight days before parturition, and the baby developed varicella at 2 days of age. In the other instance in which the baby had the eruption at birth, the mother had evidence of varicella (an "inapparent"? infection).

Since the usual incubation time of varicella averages fourteen days and may vary from ten to eighteen days, it seems certain that infections seen within eight days or less after birth are prenatal and that the virus may in certain cases pass through the placenta.

SUMMARY

Observations were reported on twins born with varicella of a mother who developed the disease the day previous to their birth.

REFERENCE

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ADRENAL CORTICAL STEROIDS IN THE MANAGEMENT OF A CASE OF MENINGOCOCCEMIA

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SINCE the advent of specific antibacterial agents, the greatest problem in the management of meningococcemia has been to keep the patient alive long enough for these agents to take effect. It has been generally accepted that toxemia with ensuing shock is responsible for early death. Shaw[1] states that the patient "needs only to survive 12 to 24 hours of profound intoxication to be almost assured of rapid and complete recovery."

It is known that the systemic manifestations of toxemia due to infectious disease are blocked by adrenal cortical steroids.[2, 3] Their mode of action is not known, but it has been suggested that these steroids act by direct intracellular effect and not by neutralization of circulating toxin or by action on the cell membrane. ACTH can also be used; it acts by stimulating the adrenals, and the final effect is the same. However, in a few rare cases the adrenals might not be capable of being stimulated (hemorrhage, exhaustion, etc.) so that the adrenal steroids themselves should be given. The emergency nature of a case of meningococcemia demands the use of the most rapidly acting available substance within this group.

In this brief case report we do not intend to discuss the routine treatment of meningococcus disease. We shall comment only on the use of adrenocortical steroids in an extremely toxic patient with meningococcemia usually classified as Waterhouse-Friderichsen syndrome. We believe that our patient's immediate clinical improvement was due to the intravenous administration of hydrocortisone, which is a very rapidly acting preparation. More slowly acting cortisone was given simultaneously by intramuscular injection in order to have the effect of this hormone available after the cessation of intravenous therapy. As this second steroid was decreased, ACTH was given for two days to stimulate the patient's own production of adrenal hormones, thus avoiding mild adrenal insufficiency which is sometimes seen even with gradual withdrawal of cortisone. We feel that it is unnecessary and undesirable to prolong the period of hormone administration beyond the time during which toxicity would persist in a case of meningococcemia treated with antibacterial agents alone.

From the Communicable Disease Department, Children's Hospital, San Francisco.

CASE REPORT

David C., a 3-year-old white male, was seen by one of us (F. B.) early in the afternoon of April 1, 1953. He was semicomatose, pale and shocky, practically moribund, and had petechiae over the entire body and in the buccal and conjunctival membranes. He was vomiting coffee-ground material. His temperature was 38.5° C. (R); the pulse was rapid and feeble; his blood pressure was not obtainable. There was only slight stiffness of the neck.

The diagnosis of meningococcemia was obvious. While arrangements for hospitalization were being made, he was given 2 Gm. of Gantrisin solution, half of this by vein, the other half intramuscularly. Three hundred thousand units of aqueous penicillin G and 900,000 units of procaine penicillin were injected together into one gluteal area, and 20 units of Lipo-Adrenal Cortex in cottonseed oil into

the other. This happened to be the only immediately available adrenal substance. He was admitted to the Communicable Disease Department of Children's Hospital, San Francisco, about one-half hour thereafter.

On admission, no significant additional findings were made except that his blood pressure was 90/60, and that his rectal temperature had risen to 40° C. He was still ashen gray and extremely ill.

After institution of therapy, the following history was obtained: The child had been well until the day prior to entry, when he developed a fever, became pale and listless, and vomited repeatedly over a period of three hours. He had then improved when aspirin was given to him. Early on the morning of admission, a "rash" was first noted by the parents. Although the fever had subsided, he complained of pains in his legs, and headache. He then ate a normal breakfast and lunch and was quite happy and playful. Shortly before he was first seen, he had again become listless, the "rash" was spreading rapidly, and his color had become poor.

Laboratory findings on admission were as follows: cerebrospinal fluid, cloudy, with 2,440 cells, 98 per cent of which were polymorphonuclear leukocytes; sugar, 77.9 mg. per cent (normal 60 to 90 mg. per cent); protein, 188.8 mg. per cent (normal 20 to 40 mg. per cent); chlorides, 692 mg. per cent (normal 720 to 740 mg. per cent). There were gram-negative diplococci visible on the direct smear. The culture showed organisms resembling meningococcus. Blood: white blood cells 24,100; polymorphonuclears 89.5 per cent with slight toxic granulation; filamented 41; nonfilamented 45.5; juvenile 3. Urinalysis: Essentially negative (specimen collected April 2). Lumbar puncture was not repeated. The total white blood count and differential count had gradually returned to normal by the time of discharge.

TABLE I

	1ST 24 HOURS	2ND 24 HOURS	3RD 24 HOURS	4TH 24 HOURS	5TH 24 HOURS	
Fluid	1,000 c.c. I.V.	1,000 c.c. I.V.	Fluids and diet in normal amounts			
Sodium	72 meq. clysis	0				
Potassium	6 meq. I.V. 4 meq. clysis	6 meq. clysis				
Sulfadiazine	1.5 Gm. clysis (sodium salt)	1.5 Gm. clysis (sodium salt)	3 Gm. orally	3 Gm. orally	3 Gm. orally	3 Gm. each 24 hr. for four days
Hydrocortisone	100 mg. I.V.	100 mg. I.V.				
Cortisone	100 mg. I.M.	100 mg. I.M.	50 mg. I.M.	25 mg. I.M.		
ACTH (gel)				80 units I.M.	80 units I.M.	

Treatment.—The treatment schedule is given in Table I. It may be noted that sodium sulfadiazine and sulfadiazine were employed despite the initial use of Gantrisin because of our greater familiarity with these drugs. Intravenous and subcutaneous fluids and medications were given at a constant rate through each twenty-four-hour period. Cortisone was injected intramuscularly at twelve-hour intervals; ACTH gel was given intramuscularly once a day.

Course.—Four hours after admission, the child's color was very much improved, and there were no new petechiae. His temperature was 37.2° C. rectally eight hours after admission. By sixteen hours, he was quite alert, but still nauseated. Twenty-four hours after admission he had two short generalized convulsions and a transient cardiac arrhythmia, thought to be due to toxic myocarditis. He was sedated with sodium pentobarbital and had no further seizures. An electrocardiogram showed no evidence of potassium deficiency. Forty-eight hours after admission he began to take and retain oral fluids; his petechiae were fading, and his neck stiffness had decreased. His improvement was rapid, and he was discharged on the eleventh hospital day. He was last seen on May 25, 1953, fifty-five days after the onset of his illness, and was entirely well.

SUMMARY

A severely toxic child with meningococcemia treated with intravenous hydrocortisone in addition to specific therapy has been presented.

The necessity for a rapidly acting, effective, "antitoxic" preparation has been discussed.

The hydrocortisone solution used in this case was supplied by Merck and Company, Inc., to Dr. Peter Forsham at the University of California Medical Center.

The authors are indebted to Dr. Forsham for making this supply available to them and for his counsel regarding its administration.

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Pediatric Therapeutics

WHAT THE PEDIATRICIAN SHOULD KNOW ABOUT THE NEWER OINTMENTS AND OINTMENT BASES

The Practical Application of Some of the Older and Newer Ointment Bases and Related Preparations in Topical Pediatric Dermatologic Therapeutics

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THE purpose of this paper is to review some of the modern concepts and trends in topical dermatologic therapeutics in infants and children, and to present the rationale for ordering topical medication. Of all the dermatologic therapeutic preparations, ointments are the most commonly prescribed remedies, as well as the most frequently abused class of preparations. Ointments are too frequently prescribed without a clear-cut indication for their use, and often are responsible for the so-called contact dermatitis[1] (dermatitis venenata) seen in infants and children. It is hoped that the discussion will serve to clarify certain misconceptions and lead to a better understanding of the underlying principles of ointment use.

DEFINITION OF AN OINTMENT

An ointment may be defined as a topical remedy of semisolid consistency, prepared by incorporating medicaments in an animal, vegetable, or mineral fat, or a synthetic chemical, and intended for local application to the skin, usually with a certain amount of friction. There are many kinds of ointments, depending upon the therapeutic purpose. Is the remedy intended for superficial effect (protection of the skin)? Or is the medicament intended to reach the epidermis, corium, subcutaneous fat, or to be absorbed by the blood stream? It is apparent that the first step in prescribing an ointment is correct diagnosis, which is followed in turn by the proper application of the therapeutic remedy. It is important for the physician to have not only a clear understanding of the dermatosis and a knowledge of the therapy indicated, but also some idea of the histopathologic structures involved. Further, it is important for the prescriptionist to understand the physical properties of the ointment bases ordered and their relative penetration into the layers of the skin.

Ointment bases are generally classified either according to their penetrability, i.e., their absorption into the various layers of the skin, or according to their composition.

CLASSIFICATION ACCORDING TO PENETRABILITY

Epidemic ointments are usually used as protectives and for prolonged contact of medication with the skin. These ointments are not absorbed by

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the skin. Petrolatum, waxes, and other hydrocarbons are used as bases for this class.

Endodermic ointments will penetrate somewhat into the epidermis and the subepidermal layers of the skin. Many of the ointments in this group contain anesthetic or antiseptic medicaments. The antihistamine creams also belong to this group. The bases used for such medicaments include the vegetable oils, lard, wool fat, hydrous wool fat, and combinations of these substances.

Diadermic ointments will yield the greatest absorption, and are represented by the polyethylene glycol bases and the oil-in-water emulsion type of base such as hydrophilic ointment, U.S.P.

INDICATIONS FOR THE USE OF EPIDERMIC, ENDODERMIC, AND DIADERMIC OINTMENT BASES

The selection of an epidermic, endodermic, or diadermic ointment base is governed by the extent of the lesions, their location, whether situated superficially or deep in the stratum corneum, epidermis, corium, or in the subcutaneous tissues. Thus, for example, in treating athlete's feet (dermatophytosis) the keratolytic remedy is best incorporated in ordinary petrolatum since the problem concerned in the proper management of this fungus infection is one in which the fungi are superficial, confined only to the stratum corneum. Keratolysis in this instance consists in causing a peeling of the dead epidermis in which the fungi live and thrive. Accordingly, it is unnecessary to use ointment bases belonging to the endodermic or diadermic types.

In the management of scabies, the scabetic female mite (*Acarus scabiei*) burrows and lays her eggs in the stratum corneum and perhaps the most superficial layer of the epidermis. Again, the ideal type of an ointment base is one belonging to the epidermic class. Precipitated sulfur incorporated in petrolatum is an excellent and efficient scabieticide. While many of the newer synthetic chemicals employed as scabieticides are now marketed in the form of a cream which will penetrate into the deeper layers of the skin, worth-while results can be obtained equally as well with sarcopticides incorporated in petrolatum alone.

When lesions are located deeper in the skin, it becomes necessary to resort to ointment bases that are more penetrating. In ecthyma, for example, the lesion involves a small portion of the corium and use can be made of an antibiotic in an ointment base of the endodermic or diadermic group in order that the penicillin or bacitracin prescribed will reach the streptococci and staphylococci located in the corium. Similarly, topical therapy for absorption and penetration into the corium in such dermatoses as erythema induratum, erythema nodosum, granuloma annulare, lesions involving the hair follicles and their sebaceous glands, the sweat ducts and their ducts, demands that the particular ointment base belongs either to the endodermic or to the diadermic group.*

Many of the hormone creams intended for systemic effect during the

*Livingood and his co-workers have recently reported (Livingood, C. S., Nilas na. S., King, W. C., Stevenson, R. A., and Mullins, J. F.: Pyogenic Infections Treated With Neomycin, J. A. M. A. **148**: 334-339, 1952) that neomycin incorporated in a water-miscible base was somewhat less effective than neomycin in a petrolatum-lanolin base. It is possible that the therapeutic effectiveness of the antibiotic in the latter base was due to the fact that most of the pyodermata in the series studied were superficial impetiginized lesions.

TABLE I. FREQUENT AND INFREQUENT DERMATOSES GENERALLY SEEN IN INFANTS AND CHILDREN WITH HISTOPATHOLOGIC SITES OF LESIONS AND TYPE OF OINTMENT BASE INDICATED

DERMATOSIS	HISTOPATHOLOGIC SITE OF LESION	THERAPEUTIC INDICATION	TOPICAL THERAPEUTIC REMEDY OF CHOICE	TYPE OF OINTMENT BASE
1. Frequent Dermatoses				
1. Impetigo contagiosa	Stratum corneum and epidermis	Germicides Antibiotics	Ammoniated mercury Penicillin Bacitracin Aureomycin	Epidermic
2. Ecthyma	Epidermis and corium	Germicides Antibiotics	Ammoniated mercury Penicillin Bacitracin Aureomycin	Endodermic Diadermic
3. Furunculosis*	Epidermis and corium	Germicides Antibiotics	Ammoniated mercury Penicillin Bacitracin Aureomycin	Endodermic Diadermic
4. Tinea circinata	Stratum corneum	Fungicidal	Iodine Ammoniated mercury Salicylic acid Undecylenic acid	Epidermic
5. Tinea capitis (animal and human types)	Stratum corneum Hair and hair follicle	Fungicidal	Iodine Ammoniated mercury Salicylic acid Undecylenic acid	Diadermic Endodermic
6. Dermatophytosis (athlete's foot)	Stratum corneum (Intraepidermal vesicles)	Fungicidal	Iodine Ammoniated mercury Salicylic acid Undecylenic acid	Epidermic
7. Scabies	Stratum corneum	Scabeticidal Sarcopticidal	Precipitated sulfur Newer synthetic chemicals "Kwell" and "Eurax"	Epidermic
8. Urticaria, lichen urticatus and erythema multiforme	Corium (blood vessels)	Antihistaminics	Pyribenzamine Benadryl	Diadermic
9. Pediculosis capitis	Hair shaft and scalp	Pediculicide	DDT-Precipitated sulfur	Epidermic
10. Atopic dermatitis	Corium and epidermis	Antihistaminics Stimulants	Pyribenzamine Benadryl Coal tar—pine tar	Diadermic(?) Endodermic
11. Seborrheic dermatitis	Epidermis and corium	Keratolytic	Salicylic acid Precipitated sulfur	Epidermic Endodermic
12. Miliaria	Corium (sweat glands and ducts) and epidermis	Keratoplastic Emollient	Lanolin	Endodermic

*A misnomer. This is generally periporitis staphylogenes in infants and children.

TABLE I—CONT'D

DERMATOSIS	HISTOPATHOLOGIC SITE OF LESION	THERAPEUTIC INDICATION	TOPICAL THERAPEUTIC REMEDY OF CHOICE	TYPE OF OINTMENT BASE
13. Pityriasis rosea	Epidermis and stratum corium	Keratolytic	Precipitated sulfur Salicylic acid	Epidermic Endodermic
14. Molluscum contagiosum	Epidermis	Keratolytic Electrocoagulation	Salicylic acid Surgical	Epidermic
15. Verruca vulgaris	Epidermis and corium	Keratolytic Electrodesiccation	Salicylic acid Surgical	Endodermic
16. Herpes simplex	Epidermis (and corium?)	Keratolytic	Salicylic acid	Epidermic
17. Herpes zoster	Epidermis (and corium?)	Keratolytic	Salicylic acid	Epidermic
18. Varicella	Epidermis	Keratolytic	Salicylic acid	Epidermic
19. Hemangioma	Corium (capillaries)	Excision Electrocoagulation Dry ice	Surgical	--
20. Cavernous angioma	Lower corium and subcutaneous tissue (blood vessels)	Excision Dry ice Radium Roentgen ray	Surgical	--
21. Acne vulgaris	Perifolliculitis (epidermis and corium)	Keratolytic	Sulfur Salicylic acid	Diadermic Endodermic
	2. Less Frequently Seen Dermatoses			
1. Erythema nodosum	Upper portion of subcutaneous tissue (blood vessels) also corium	Antiphlogistic (?) Alterative	Mercurial ointment Iodine	Diadermic
2. Erythema induratum	Lower corium and subcutis (blood vessels)	Antiphlogistic (?) Alterative	Mercurial ointment Thymol iodide	Diadermic
3. Psoriasis	Epidermis and papillary bodies	Keratolytic Antipsoriatic	Ammoniated mercury Salicylic acid Chrysarobin	Epidermic
4. Lichen planus	Epidermis and upper corium	Alterative	Mercury salicylate	Endodermic
5. Lupus erythematosus	Epidermis, corium (dermal appendages	Antihistaminics Stimulants	Pyribenzamine Benadryl	Diadermic
			Sulfur-salicylic acid Ichthammol	Diadermic
6. Lichen scrofulosorum	Upper corium (hair follicles)	Vitamins Alterative Stimulant	Vitamins A and D Cod liver oil Thymol	Diadermic
7. Sarcoid	Boeck's-corium Darier-Roussy's-subcutaneous tissue	Stimulant Alterative	Ichthammol Cod liver oil	Diadermic
8. Granuloma annulare	Corium	Keratoplastic Stimulant	Salicylic acid Pine tar ointment	Diadermic

TABLE I—CONT'D

DERMATOSIS	HISTOPATHOLOGIC SITE OF LESION	THERAPEUTIC INDICATION	TOPICAL THERAPEUTIC REMEDY OF CHOICE	TYPE OF OINTMENT BASE
9. Ichthyosis	Epidermis and appendages (sebaceous and sweat glands in severe cases)	Keratoplastic Emollients	Salicylic acid Cocoa butter, lard, goose grease, almond oil, olive oil, etc.	Diadermic
10. Keratoderma palmaris et plantaris	Epidermis and corium (?)	Keratolytic (strong) Alterative	Salicylic acid Mercurial ointment	Epidermic Endodermic
11. Epidermolysis bullosa hereditaria	Epidermis and corium	Protective Astringent	Zinc oxide ointment	Epidermic
12. Kaposi's varicelliform eruption	Epidermis and corium	Antibiotics	Aureomycin	Diadermic
13. Variola	Epidermis and corium	Keratolytic	Salicylic acid	Epidermic
14. Keratosis follicularis (Darier's disease)	Epidermis and corium	Keratolytic Vitamins	Sulfur, salicylic acid Resorcin	Endodermic
			Vitamin A ointment	Diadermic
15. Dermatitis herpetiformis (Duhring's disease)	Epidermis and corium	Keratolytic Stimulant	Sulfur Oil of cade	Endodermic
16. Avitaminosis A	Epidermis and corium (sweat and sebaceous glands in severe cases)	Vitamins Emollients	Vitamin A ointment Olive oil, cod liver oil, almond oil, goose grease	Diadermic
3. Dermatoses Seldom Encountered (Rare)				
1. Xeroderma pigmentosum	Epidermis and corium	Sun screen (protective)	Phenyl salicylate Titanium dioxide	Epidermic
2. Hydroa aestivale	Epidermis and corium	Sun screen (protective)	PABA Menthyl salicylate	Epidermic
3. Favus	Perifollicular area in corium	Fungicidal	Chrysarobin Citrine ointment Ammoniated mercury	Diadermic
4. Lupus vulgaris (rare in United States)	Upper corium (mostly) Secondary epidermis	Antibiotic	Streptomycin	Diadermic

TABLE II. RELATIONSHIP OF COMPOSITION TO PENETRATION

COMPOSITION	PENETRATION	EXAMPLE
Hydrocarbon bases	Epidermic	Petrolatum, paraffin
Oleaginous bases	Epidermic to slight endodermic	Olive oil, lard
Water-in-oil bases	Somewhat endodermic	Lanolin, hydrophilic petrolatum, U.S.P.
Oil-in-water bases	Endodermic to diadermic	Hydrophilic ointment, U.S.P.
Soluble bases	Easily endermic and diadermic	Carbowaxes, polyethylene glycols

climacteric period and for the treatment of acne during adolescence, and vitamin creams (A and D) contain Carbowax as their bases. The old-fashioned oleate of mercury and the mercurial rubs (mercurial ointment dispensed in waxed papers) are examples of medications that were prescribed for the systemic effects of mercury in the treatment of syphilis.

In order to appreciate the particular applications of each type of ointment base, it is necessary to understand the histopathologic pictures of the dermatoses being treated. The outline given in Table I briefly summarizes the location of the more common dermatoses of infants and children and is helpful in selecting the type of ointment base required.

OINTMENT BASES CLASSIFIED ACCORDING TO COMPOSITION AND PHYSICAL CHARACTERISTICS

1. Hydrocarbon bases. Examples are petrolatum, liquid petrolatum, and paraffin.
2. Oleaginous bases. These are fats and waxes.
3. Emulsion bases. Water-in-oil emulsions are produced when water is absorbed by certain bases such as hydrophilic petrolatum, U.S.P. Oil-in-water emulsions such as hydrophilic ointment, U.S.P.
4. Soluble bases. Polyethylene glycols, Carbowaxes.

DISCUSSION OF OINTMENT BASES

Hydrocarbon Bases. — Petrolatum, U.S.P., is a purified, semisolid mixture of hydrocarbons of yellowish to light amber color obtained from petrolatum. Used topically, it covers and protects the skin from external irritants. Being completely inert chemically, it is compatible with any medicaments that may be incorporated in it and is not subject to rancidity. The major disadvantages are its greasy nature, leading to difficulty in removing petrolatum from skin and clothing, and its inability to absorb more than about 5 per cent of water.

Petrolatum alone is not suitable as a base for ointments to be used in exudative skin lesions since it tends to trap the exudation giving rise to an acute eczematoid dermatitis. For such a purpose pastes or hydrophilic petrolatum are indicated.

Although petrolatum is ordinarily regarded as an innocuous substance, it can occasionally cause sensitization of the skin.[2] Furthermore, it is an ingredient of many commercial products such as Aquaphor (Duke), Dermovan (Texas Pharmacal Co.), Albolene Cream (McKesson), Greaseless Ointment Base (Burroughs Wellcome), Hydrosorb (Abbott), Qualatum (Almay), and Unibase (Parke, Davis). Many of the so-called nonallergic or hypoallergic cosmetic creams and many of the newer emulsion bases contain petrolatum or mineral oil. The Almay emulsion base is entirely free of petrolatum or mineral oil.

White petrolatum, U.S.P., is petrolatum that has been decolorized by various means such as solvent extraction or percolation through bone black or absorptive clay. It has been customary to use white petrolatum in the preparation of ointments containing colorless or white ingredients.

White ointment and yellow ointment are recognized by the United States Pharmacopeia as bases for the preparation of several official ointments. White ointment contains 95 per cent white petrolatum and 5 per cent

white wax; yellow ointment contains the same proportions of yellow petrolatum and yellow wax. These products formerly contained 5 per cent of wool fat.*

Paraffin, N.F., is closely related chemically to petrolatum, being a mixture of solid hydrocarbons obtained from petroleum. It is used only to stiffen ointments.

Oleaginous Bases.—Lard is less popular today than formerly, principally because of the ease with which it becomes rancid under the influence of moisture, air, and light. Through oxidation and hydrolysis, the esters of lard are decomposed to various peroxides, ketones, aldehydes, and acids which are malodorous and irritant.

Benzoinated lard, N.F., contains certain acids and esters extracted from Siam benzoin. These substances, in addition to providing a pleasant aroma, serve as antioxidants, being themselves more easily oxidized than the fat. Newer bases penetrate as well as lard and are more stable.

Suet, N.F., is the internal fat of the abdomen of the sheep. It is much firmer in consistency than lard and finds little use in the preparation of ointments.

Hydrogenated vegetable oils. When certain liquid vegetable oils containing unsaturated linkages are hydrogenated, and thus converted to saturated compounds, they become soft, unctuous solids, suitable for use as ointment bases. Examples of such products are Crisco and Spry, originally manufactured for culinary use. The reaction involved is essentially as follows:

$$R.CH:CH.R \xrightarrow{H_2} R.CH_2.CH_2R.$$

Theobroma oil, U.S.P. (cacao butter, cocoa butter), is the fat obtained from the roasted seeds of *Theobroma cacao*. Although used principally as a suppository base, this yellowish white solid is also valuable in dermatology as an emollient and as a component of skin creams.

Beeswax is used to increase the firmness of ointments. The United States Pharmacopeia recognizes both yellow wax and white wax, the latter having been bleached by oxidizing agents such as potassium permanganate or peroxides. White wax is somewhat more flaky than yellow.

Spermaceti, U.S.P. (cetaceum), obtained from the head of the sperm whale, occurs as a white, somewhat translucent, slightly unctuous mass. It gives firmness and velvety sheen to ointments. Spermaceti will penetrate the skin slightly.

Emulsion Bases.—These may be of the water-in-oil, or the oil-in-water type. Certain bases are capable of taking up water or aqueous solutions to form stable water-in-oil (w/o) emulsions retaining the characteristic consistency of ointments. Because of this ability to absorb water, they are called absorption bases, an unfortunate term in view of the dermatologist's interest in skin penetration and absorption. In these products the water is dispersed throughout the oil, the latter being the continuous (external) phase and causing the products to be greasy to the touch.

*Wool fat has been deleted from formulas in the U.S.P. XIV because of sensitization reported by some dermatologists, a fact very much overestimated in the opinion of one of the writers (H. H. P.). In a large practice which covers a period of over thirty years, the writer has encountered only a single instance of sensitivity to wool fat. However, wool fat will remain official per se so that it may be used by physicians when indicated.

In the oil-in-water (o/w) type of emulsion bases, known as washable bases, the oil is dispersed through the aqueous phase, leading to a product that mixes with water and is easily removed from the skin or clothing by washing.

Wool fat, U.S.P., also known as anhydrous lanolin, is a classic example of an absorption base. It owes its water-absorbing power to the presence of cholesterol and related sterols, about 7 per cent of which are in the free state, the rest as esters of high

TABLE III. FORMULAS FOR ABSORPTION BASES

Hydrophilic Petrolatum, U.S.P.	
White Petrolatum	86 Gm.
Stearyl Alcohol	3 Gm.
White Wax	8 Gm.
Cholesterol	3 Gm.
Ointment of Wool Alcohols British Pharmacopoeia	
Wool Alcohols	3 Gm.
Paraffin	12 Gm.
White Petrolatum	5 Gm.
Liquid Petrolatum	30 c.c.
Aquabase (University of Iowa Hospital)	
Cholesterol	3 Gm.
Cottonseed Oil	6 Gm.
White Petrolatum	91 Gm.
Arlacel Absorption Base	
Arlacel C (Atlas Powder Co.)	5.0 Gm.
White Wax	2.5 Gm.
Petrolatum	30.0 Gm.
Liquid Petrolatum	13.0 Gm.

molecular weight fatty acids. A mixture of these alcohols (sterols) is commercially available as wool alcohols and is used like wool fat to impart water-absorbing properties to ointment bases.

Wool fat occurs as a brownish yellow, tenacious, unctuous mass, with not more than a slight odor of wool. It belongs to the endodermic group of ointment bases. Wool fat will pick up twice its weight of water, forming a water-in-oil emulsion.

Hydrophilic petrolatum, U.S.P., was formulated to provide a modern absorption base of good quality prepared from easily available, standardized ingredients. It is capable of taking up twice its own weight of water without difficulty. The base should be heated just sufficiently to melt it and the water or aqueous solution, at room temperature, added in small portions with constant agitation.

Formulas for hydrophilic petrolatum and other absorption bases are given in Table III. The Arlacel C used in one of these formulas is an emulsifying agent comprising a fatty acid ester of hexitol anhydride.

Ingredients of Modern Bases.—Cetyl Alcohol, N.F., known also as palmityl alcohol, is principally $CH_3(CH_2)_{14}CH_2OH$, the rest consisting of other solid alcohols normally present in the natural esters from which the product is obtained. Cetyl alcohol is usually supplied as white, unctuous flakes or granules. In conjunction with a suitable surface-active agent such as sodium lauryl sulfate it aids the preparation of stable oil-in-water emulsion bases.

Cholesterol, U.S.P. Cholesterol ($C_{27}H_{45}OH$) is a steroid alcohol. It occurs as white or faintly yellow, almost odorless, pearly droplets or granules, and is found widely distributed in all animal fats, yolk of eggs, brain, milk, fish oils, wool fat (10 to 20 per cent), etc. Cholesterol, when added to fats or hydrocarbons, produces absorption bases, products capable of taking up water to produce emulsions.

Cholesterol is devoid of sensitization and may be used in place of wool fat in those instances where wool fat causes sensitization.

Methylparaben and propylparaben are, respectively, the methyl and propyl esters of parahydroxybenzoic acid. These are preservatives, the first being effective against molds, the latter against yeasts.

Sodium lauryl sulfate, U.S.P. (sodii laurylis sulfas), is available under its official name and also under a variety of trade-names such as Gardinol WA, Duponol C, and Irium. It is a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate, $(CH_3[CH_2]_{10}CH_2O\ SO_3Na)$. Sodium lauryl sulfate occurs as small, white or light yellow crystals, having a slight characteristic odor, or as a white powder. It is an anionic surface-active agent used in many cosmetic preparations as an emulsifying and wetting agent. It is quite soluble and is used in very small quantities in aqueous solutions.

Spans and Tweens are nonionic surface-active agents supplied by Atlas Powder Company. The Spans are partial esters of such fatty acids as lauric, palmitic, stearic and oleic, with hexitol anhydrides derived from sorbitol. The Tweens are derived from the Spans by adding polyoxyethylene chains to the nonesterified hydroxyls. The Spans, therefore, are esters while the Tweens are the same esters modified by adding on, through an ether linkage, additional water-solubilizing chains. Spans tend to be oil-soluble while Tweens tend to be water-soluble. Considerable modification of these tendencies, however, can be induced by suitable balance and adjustment of the lipophilic (oil-loving) fatty acid residues and the hydrophilic (water-loving) hexitol residue and polyoxyethylene chains.

Stearyl alcohol, U.S.P., is a mixture of solid alcohols consisting principally of stearyl alcohol, $CH_3(CH_2)_{16}CH_2OH$. In appearance and properties, it is similar to cetyl alcohol. Both alcohols impart some degree of luster to ointments.

Washable bases, being oil-in-water emulsions in which each oil particle is completely surrounded by water, do not display the greasiness of the absorption bases. They are easily washed from the skin or clothing with water.

In a sense, these washable emulsion bases represent an extension of the older vanishing cream type of product. The classic vanishing cream is a mixture of potassium, ammonium, or sodium stearate with water, holding in emulsified form some free stearic acid. Glycerin or other hygroscopic agent is used to prevent drying out. A basic formula is:

Stearic Acid	12.0 Gm.
Glycerin	5.0 c.c.
Potassium Hydroxide	0.5 Gm.
Water	32.0 c.c.

Vanishing creams of the glyceryl monostearate type have the advantage of greater ease of manufacture and improved keeping qualities. A type product is:

Glyceryl Monostearate SE	6.0 Gm.
Spermaceti	2.5 Gm.
Glycerin	2.5 c.c.
Water	38.0 c.c.
Methylparaben	0.06 Gm.

The SE indicates "self-emulsifying" and designates a glyceryl monostearate to which a stearate soap or other surface-active agent has been added.

A major disadvantage of vanishing cream as a vehicle is its lack of com-

patibility with so many of the medicinal agents employed by the dermatologist. Strong electrolytes (ionizing salts), acids, and alkalies lead to decomposition, usually with the separation of water and/or the development of a granular appearance. This disadvantage has been largely overcome in the modern washable bases.

Hydrophilic ointment, U.S.P., is a good example of a modern emulsion base of the oil-in-water type. It is compatible with a wide range of medicaments, does not become rancid or undergo bacterial decomposition, and is water-washable. As shown in Table II, such ointments are endodermic and diadermic, i.e., medication contained in them penetrates deeply into the corium and subcutaneous tissues and can be picked up in the circulation. Formulas for washable bases are given in Table IV.

TABLE IV. FORMULAS FOR WASHABLE BASES

Hydrophilic Ointment, U.S.P.	
Stearyl Alcohol	25 Gm.
White Petrolatum	25 Gm.
Propylene Glycol	12 Gm.
Sodium Lauryl Sulfate	1 Gm.
Methylparaben	25 mg.
Propylparaben	15 mg.
Water	37 Gm.
Beeler Base (J. A. Ph. A. Prac. Ed. 3: 231 [July] 1942)	
Cetyl Alcohol	15.0 Gm.
White Wax	1.0 Gm.
Propylene Glycol	10.0 Gm.
Sodium Lauryl Sulfate	2.0 Gm.
Water	72.0 c.c.
Gibson Base	
Sodium Lauryl Sulfate	1.0 Gm.
Cetyl Alcohol	10.0 Gm.
White Petrolatum	40.0 Gm.
Water	43.0 Gm.
Carbowax Emulsion Base	
Cetyl Alcohol	25.0 Gm.
Carbowax 1500	25.0 Gm.
Sodium Lauryl Sulfate	1.0 Gm.
Water	49.0 c.c.
Span and Tween Base Containing Stearic Acid	
Stearic Acid	12.0 Gm.
Span 60	10.0 Gm.
Tween 60	6.0 Gm.
Water	72.0 c.c.

INDICATIONS FOR OIL-IN-WATER AND WATER-IN-OIL TYPES OF EMULSIONS

The oil-in-water (o/w) type of emulsion base is indicated when greater penetration into the skin (corium and subcutaneous tissues) is desired and when systemic effect (absorption) is required for the larger blood vessels are located in the midcorium and the lowermost portion of the corium and in the subcutaneous tissues. On the other hand, the water-in-oil (w/o) type of emulsion is an excellent preparation when an emollient effect is desired. Many of the dermatoses seen in infants and children are accompanied by a dryness of the skin. Lack of sebaceous secretion may be either caused by a congenital disorder (xerosis, ichthyosis vulgaris) or acquired (avitaminosis A). Dryness of the skin is also seen in many dermatoses such as atopic dermatitis (lichenification), etc. A dry skin calls for the use of emollients of which the water-in-oil (w/o) type of emulsions is representative.

The greater absorption of medicaments when applied in emulsion bases frequently calls for a reduction in the concentration of the active medicament ordered.[3] Thus, such chemicals as boric acid, ammoniated mercury, and coal tar derivatives may lead to toxic symptoms when applied over extensive areas of the skin.[4] Accordingly, frequent urinalyses should be carried out routinely when such remedies are prescribed.

Soluble Bases.—The polyethylene glycols (Carbowaxes) constitute a group of greaseless bases which are completely water-soluble and possess the greatest endodermic and diadermic effect. The polyethylene glycols are liquid, solid or semisolid, depending

upon their molecular weight. The higher the molecular weight, the more solid the preparation. Thus, the polyethylene glycols having a molecular weight up to 1,000 are liquid, those having a molecular weight between 1,000 and 2,000 are semisolid and those having a molecular weight above 2,000 are solids. The trade name "Carbowax" is applied to the solid compounds. The average molecular weight is indicated by the number associated with the name, thus Carbowax 1500, Carbowax 4000, etc.

Polyethylene glycol ointment, U.S.P., consists of a mixture of equal parts of polyethylene glycols 400 and 4000. It is a water-miscible (i.e., soluble) ointment base showing essentially no incompatibilities with dermatologic medicaments. By varying the ratio of liquid, semisolid, and solid polyethylene glycols, it is possible to control precisely the consistency of the resultant base. The softening induced by some ingredients such as organic acids and phenol can be overcome by the inclusion of 5 per cent of cetyl alcohol. Not more than 3 per cent water can be added without liquefaction.

Suppositories made with Carbowaxes are becoming popular since their use ensures that the medicaments ordered will be dissolved in the rectum and absorption encouraged.

Pastes.—When a powder and an ointment are combined in equal proportions, the composition of the newly formed preparation acts differently from an ointment. Such a preparation is called a *paste* and is remarkable for its potential absorptive property. A paste, because it is porous, takes up fluids and exudates much as a sponge absorbs water.

Pastes differ from ointments in having a much higher percentage of powder, usually either talc or starch. Some pastes have as much as 70 per cent of powder, this causing them to exert a drying effect upon the skin.

Lassar's plain zinc paste (zinc oxide paste, U.S.P.) named after Lassar, the German dermatologist, is made up of 25 per cent zinc oxide, 25 per cent starch, and 50 per cent white petrolatum. It thus contains two and a half times the amount of powder contained in zinc oxide ointment, the latter representing 20 per cent of zinc oxide in white ointment and liquid petrolatum. The starch in Lassar's paste contributes a different texture than is obtained with zinc oxide alone.

A paste will take up many kinds of medication. However, when drugs are incorporated into pastes, they show lesser activity than when embodied in ointments. Pastes do not lend themselves to application by rubbing; they are best applied on gauze.

Pastes are particularly useful in exudative dermatoses, as, for example, in the second state of atopic dermatitis (infantile eczema) when most of the fluid has been drained from the epidermis and corium, but there is still some residual fluid remaining. It is in this interim stage, the subacute stage, that pastes are most useful.

Snapp's unpublished data, quoted by Rothman and Shapiro,[5] has shown that under experimental conditions ointments suppress insensible perspiration 90 per cent and pastes only 70 per cent.

Petroxolins.—Petroxolins represent emulsion bases, liquid or solid, containing liquid petrolatum emulsified

with the aid of ammonium oleate prepared by reaction of oleic acid and strong ammonia solution. The inclusion of wax in the formula permits the preparation of semisolid products having some of the characteristics of washable ointment bases. Petroxolins are excellent solvents and carriers for many medicaments used externally; they are intended for topical use and are readily absorbed by the skin. They are marketed under the trade name of Petrogen. The British Pharmaceutical Codex Title for this group of preparations is Parogen.

Only one petroxolin is official in the National Formulary IX. This is solid petroxolin (Petroxolinum spissum), known also as solid petrox, and prepared from light liquid petrolatum, yellow wax, oleic acid, strong ammonia solution, lavender oil, and alcohol. It is a useful vehicle for balsamic resins such as balsam of Peru. Frequently, when Peruvian balsam is incorporated in an ointment, it tends to separate in granular particles which might be irritant to the skin. Solid petroxolin lends itself nicely to the preparation of ointments of Peruvian balsam.

Other petroxolins, once recognized by the National Formulary and of dermatological interest and usefulness, include iodine petroxolin, mercury petroxolin, betanaphthol petroxolin, cade petroxolin, diluted iodine petroxolin, ichthammol petroxolin, and methyl salicylate petroxolin.

SUMMARY

1. The development of newer type ointment bases, particularly the emulsion bases and the soluble bases, has led to new concepts of ointment therapy.

2. On the basis of their degree of penetration, ointments can be classified as epidermic, endodermic, and diadermic.

3. For a rational understanding of the applicability of the different types of ointment bases, the pediatrician needs a sound knowledge of the histopathologic factors underlying the more common dermatoses encountered in children.

4. Accordingly, some of the newer trends in topical dermatologic therapy have been described and explanation given of the use of the newer bases to obtain optimum therapeutic effect.

5. The skin must be recognized as a functioning organ and a barometer of general health.

6. It is hoped that this paper will be useful to pediatricians and to general practitioners in their routine care of children and that it will stimulate interest in the use of official agents.

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DIAGRAM ILLUSTRATING MECHANISM OF PENETRATION OF VEHICLES AND MEDICATIONS THROUGH THE SKIN (SIMPLIFIED)

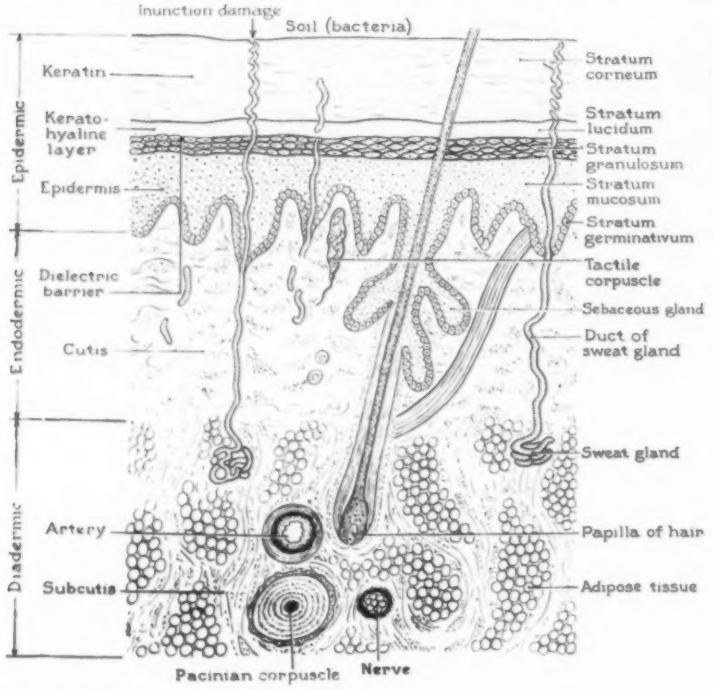

Chart I.

Figs. 1 and 2.—Photomicrographs of the normal skin of a 6-day-old female (face) (Fig. 1) in comparison with the normal skin of an adult (Fig. 2). Note the stratum corneum is poorly developed (lacy appearance) in the infant's skin in contrast to a well-defined barrier of the stratum corneum in the adult. It is the immature layer of stratum corneum in the infant which renders the skin vulnerable and accounts for the frequency with which vesiculation is seen more often in infants from topical medication than in older children and adults. Accordingly, in prescribing topical medicaments for infants and for younger children mild concentrations of remedial agents should be ordered at first and the strength of the medicaments cautiously increased as a tolerance to the skin develops. To minimize against the potential danger of a dermatitis venenata (contact dermatitis—overtreatment dermatitis, therapeutic dermatitis) zinc oxide 10 to 20 per cent should be added to the ointment base or zinc oxide ointment used.

Fig. 3.—Photomicrograph of impetigo contagiosa. Note the lesion which consists of a subcorneal vesicle filled with polymorphonuclear neutrophils. The bulla is situated high up in the epidermis. After removing the crusts by the keratolytic use of soap and warm water, a simple ointment consisting of 2 per cent ammoniated mercury (white precipitate) in a petrolatum base or an antibiotic such as penicillin or bacitracin in petrolatum should be applied at relatively frequent intervals and is generally all that is required to effect a cure. There is no need for ointment bases of the endodermic and dialdermic type since the lesion is confined entirely to the most superficial layers of the epidermis. For similar reasons intramuscular injections of penicillin are not necessary for "cure" of impetigo contagiosa.

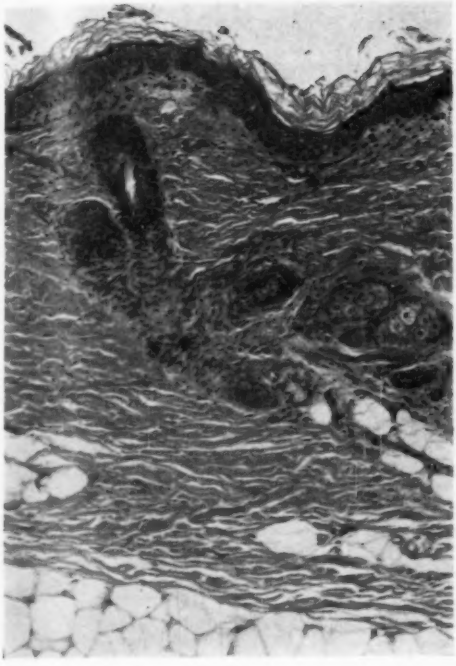

Fig. 1.

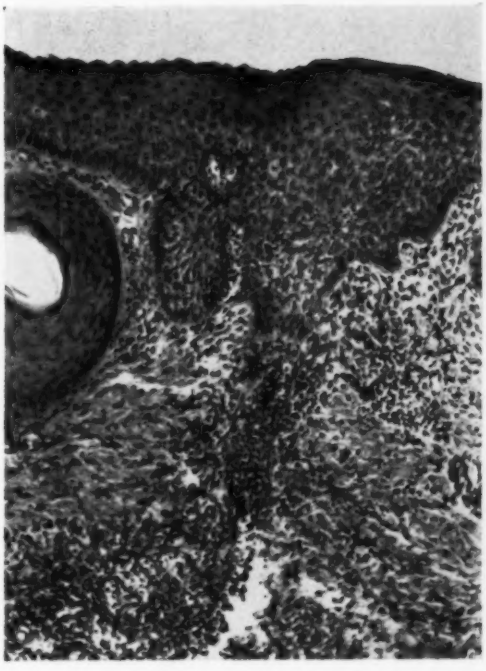

Fig. 2.

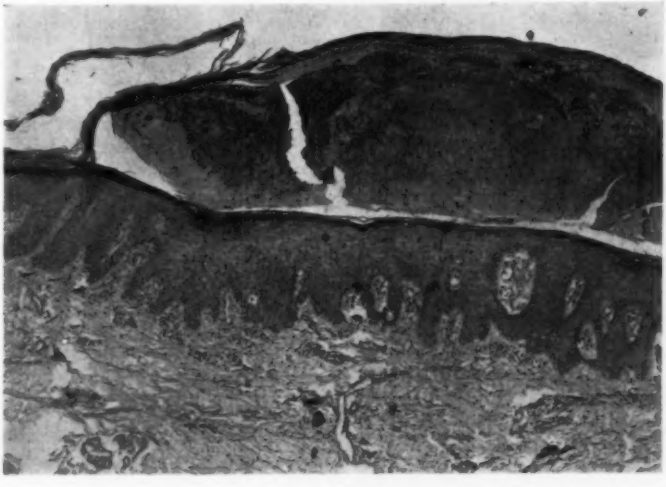

Fig. 3.

(For legends, see opposite page.)

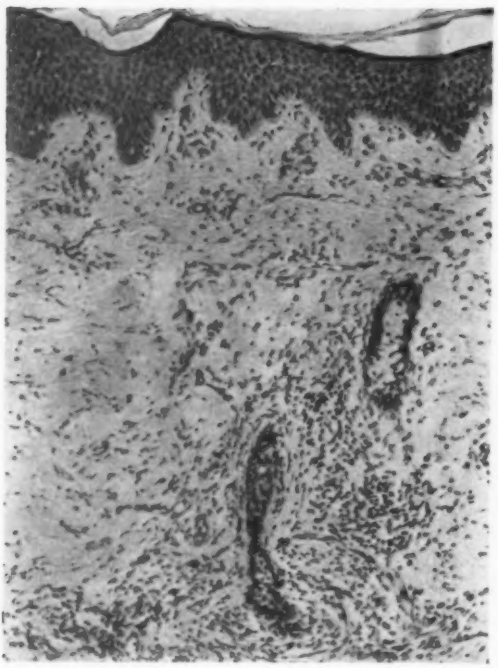

Fig. 4.

Fig. 5.

Fig. 4.—Photomicrograph of ecthyma. In contrast to the lesions seen in impetigo contagiosa, the lesions in ecthyma are deeper and have invaded the corium. For optimum therapeutic effect the bactericidal remedy (ammoniated mercury 2 to 3 per cent) should be incorporated in an ointment base of the endodermic type such as hydrophilic petrolatum, U.S.P., which is a water-in-oil type of emulsion base. Antibiotics to be effective should also be ordered in a water-in-oil emulsion type of base. Therapeutic remedies added to petrolatum are relatively ineffective in many dermatoses involving the corium. Intramuscular injections of penicillin in oil or in aqueous menstra are definitely indicated early in the therapeutic regime of ecthyma.

Fig. 5.—Photomicrograph of a subcutaneous abscess of the skin of a young Negro infant seen in an overheated nursery. Clinically, the skin of the entire body and the scalp and extremities were covered with various-sized pustules. Such a condition in patients is frequently misdiagnosed as "furunculosis." The upper cutis vessels are all very dilated and show a mild, inflammatory cellular, banal, perivascular reaction. Histopathologically, the outstanding feature is the large mass of granulation tissue involving the subcutaneous fat mainly and to a certain extent, the deeper portions of the cutis. A considerable number of sweat glands are involved in the process. The mass of granulation tissue infiltrates the fat trabecularly and is made up of enormous numbers of polymorphonuclears, epitheloid cells, plasma cells, hydroblastic and fibroblastic cells. The tissue in the center of the mass has gone on to abscess formation with total disintegration and contains fibrin and red blood cells. Diagnosis: Periporitis staphylogenes with abscess of the subcutis area. Antibiotics are called for by intramuscular injection. Topically, bactericidal remedies and antibiotic therapy should be incorporated in an ointment base belonging to the endodermic and diadermic class (hydrophilic petrolatum, U.S.P.; hydrophilic ointment, U.S.P.; or polyethylene glycol ointment, U.S.P., for optimum therapeutic effect).

Fig. 6.—Photomicrograph of erythema nodosum. Note that the inflammatory reaction is deep, i.e., confined for the most part to the fat cells (around the blood vessels in the fat) which consist mostly of a cellular infiltrate of neutrophils and lymphocytes. Topical remedial agents should be incorporated in an endodermic or diadermic ointment type of base for optimum therapeutic effect.

Fig. 7.—Photomicrograph of lupus vulgaris. The histopathologic section shows an active infiltrate consisting of tubercles with epitheloid cells, giant cells, and a peripheral zone of lymphocytes located in the corium and subcutaneous tissue. Secondary changes in the epidermis are not uncommon. Lupus vulgaris is more frequently seen in European countries than in the United States. Topical therapy such as dihydroxystreptomycin should be prescribed in an ointment base belonging to the endodermic and diadermic class for optimum therapeutic effect.

Fig. 8.—Photomicrograph of skin in a scabetic patient. Histopathologic section showing burrows, the acarus with its ova and scybala (excreta) deposited in the stratum corneum. Note the burrow is confined almost in its entire length to the horny layer of the epidermis. While many of the newer synthetic scabieticides are marketed in a vanishing cream type of ointment base, the simple application of 6 per cent precipitated sulfur (children) in petrolatum is equally efficacious for treatment since here a superficial effect and not one of penetration into the corium is sought due to the location of the *Acarus scabiei* and its ova in the stratum corneum. (From the private collection and by courtesy of Dr. Reuben Friedman.)

Fig. 9.—Photomicrograph of skin in a scabietic patient, showing burrows. The acarus with its ova and scybala (excreta) deposited in the stratum corneum. (From the private collection and by courtesy of Dr. Reuben Friedman.)

Fig. 6.

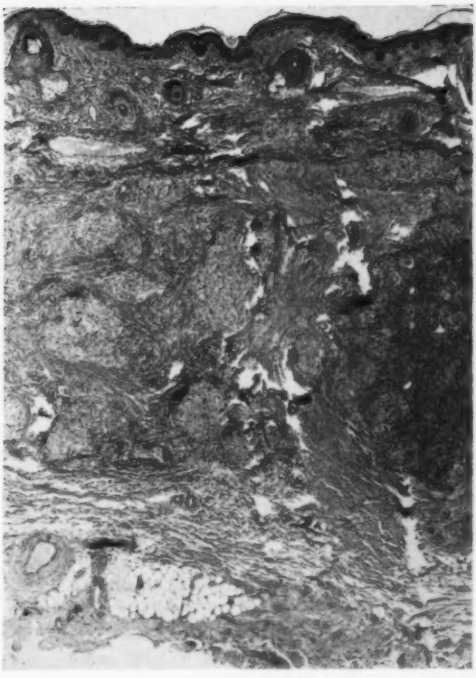

Fig. 7.

Fig. 8.

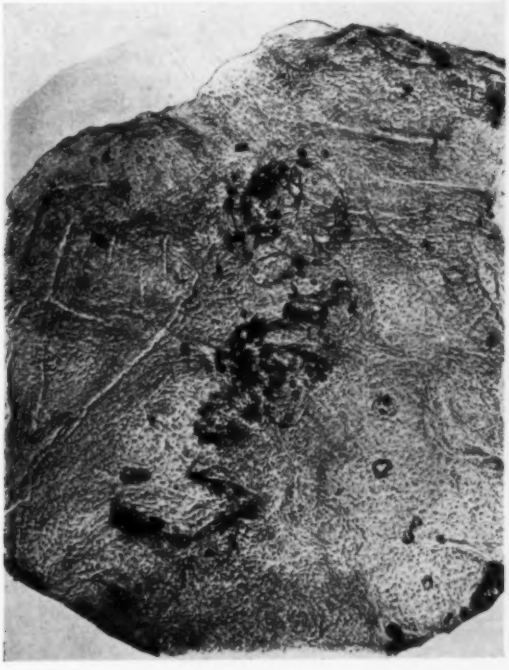

Fig. 9.

(For legends, see opposite page.)

USEFUL SUGGESTIONS IN PRESCRIBING TOPICAL REMEDIES FOR INFANTS AND CHILDREN (10 USEFUL RULES)

1. Never prescribe a remedy without a clear-cut indication. If you must order an ointment or topical remedy, prescribe such remedies that you are sure will do no harm, i.e., Burow's paste, consisting of aluminum acetate, 10 parts; anhydrous lanolin, 20 parts; zinc oxide paste, 30 parts. Always inquire as to wool sensitivity. Avoid the use of lanolin in wool-sensitive patients. It should be remembered that many of the simpler disorders are frequently worsened and traumatized through the indiscrete use of topical remedies or through self-medication.

2. In prescribing topical remedial agents, follow the good rule: *The more acute the dermatosis, the milder the topical therapy.*

3. Use simple remedies. All topical remedies should be prescribed at first in mild concentration and increased in concentration gradually as indicated. Lane, Gaul, Miller, and many others have referred to the contact dermatitis resulting from the indiscrete use of topical remedies calling it "therapeutic dermatitis," "overtreatment dermatitis," etc. Among these remedies may be listed: tar, mercury, iodine, salicylic acid, phenol, menthol, benzoic acid, Nupercaine, Butyn, and the sulfonamides, many of which are definitely skin sensitizers.

4. Choose the proper remedy in terms of the existing cutaneous disorder. When edema is present (any dermatosis, irrespective of cause) characterized by erythema, vesiculation, oozing of the skin, pain, and local discomfort (burning sensation), use continuous wet dressings—not ointments—until the acute signs have subsided (24-48-72 hours). The subacute phase of any dermatosis requires the use of soothing remedies, pastes in preference to ointments (pastes absorb residual fluid as a sponge absorbs water). The chronic phase calls for remedies that are stimulating; examples, the tars, salicylic acid, or perhaps a mild dose of roentgen ray.

5. Know the composition of the ointment or topical preparation you order.

6. Prepare the skin properly. Always treat a "sick skin" with gentleness, never harshly. For cleansing, a starch bath is excellent, also emollients (slightly warmed) and applied with absorbent cotton; examples, olive oil, sweet almond oil, peanut oil, mineral oil. On the other hand, ordinary soap frequently irritant to a "sick skin" is best avoided, but superfatted soaps such as basis soap (Duke) and hyperoilated soap (Stiefel) unscented, may serve usefully. Sulfonated soaps are useful too.

7. For generalized dermatoses baths are generally preferred to ointments. Shake lotions are always serviceable.

8. Avoid insofar as is possible the use of ointments over extensive lesions in hot weather. Shake lotions (evaporating lotions) are often serviceable.

9. Avoid the use of boric acid as a wet dressing and boric acid ointment in the treatment of infants and younger children, particularly when a large area is involved, and when extensive acute inflammatory lesions are present.

10. Avoid the use of proprietary preparations of unknown composition and expensive drugs when remedial agents in the U.S.P. and the N.F. can be used.

REPRESENTATIVE PRESCRIPTIONS

1. *Antipruritic Ointment*

Camphor	1.0 Gm.
Phenol	1.0 Gm.
Eucalyptol	0.2 c.c.
Calamine	5.0 Gm.
Zinc Oxide	5.0 Gm.
Rose Water Ointment	100.0 Gm.

Misce et fiat unguentum.
Signa: Apply three or four times daily.
Indication: Antipruritic—antiphlogistic.

Menthol	0.02 Gm.
Olive Oil	0.5 c.c.
Hydrous Wool Fat q.s. ad	20.0 Gm.

Misce et fiat unguentum.
Signa: Local application.
Indication: Pruritic dermatoses.

2. *Sulfur Salicylic Acid Ointment*

Precipitated Sulfur 3.0 Gm.
Salicylic Acid 3.0 Gm.
Castor Oil 5.0 c.c.
Petrolatum q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Apply by inunction into the scalp (skin).
Indication: Keratolytic (seborrheic dermatitis of scalp).

3. *Antiscabietic Ointment*

Precipitated Sulfur
Peru Balsam
Castor Oil aa 6.0 Gm.
Hydrous Wool Fat
Petrolatum aa q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Scabieticidal—active treatment.

4. *Modified Wilkinson Ointment*

Pine Tar
Precipitated Sulfur* aa 20.0 Gm.
Soft Soap
Petrolatum aa 60.0 Gm.
Indication: For treatment of scabies and dry disseminated atopic dermatitis (eczema) (Lust-Levinsohn.)

5. *Pine Tar Ointment (Antieczematous Ointment)*

Pine Tar Ointment, U.S.P. 8.0-30.0 Gm.
Zinc Oxide Ointment 60.0 Gm.
Misce et fiat unguentum.
Signa: Constant application.
Indication: Stimulant (chronic stage).
Initial treatment should begin with milder strength of the tar ointment and increased gradually as a tolerance to the skin is obtained.

6. *Crude Coal Tar Ointment*

Crude Coal Tar
Zinc Oxide
Castor Oil aa 8.0 Gm.
(Mix the ingredients and allow to remain exposed to the air for 24 hours, then add)
Starch 60.0 Gm.
Petrolatum 54.0 Gm.
Misce et fiat unguentum.
Signa: Constant application.
Indication: Stimulant—chronic eczema.

7. *Keratolytic-Stimulating Ointment*

Precipitated Sulfur 3.0 Gm.
Salicylic Acid 3.0 Gm.
Liquor Carbonis Detergens 5.0 c.c.
Greaseless Ointment Base q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Apply several times daily.
Indication: Chronic dermatitis.

8. *Soft Ointment (Unguentum Molle) Unofficial*

White Petrolatum
Wool Fat* aa 30 Gm.
Signa: Apply locally.
Indication: A soft, mild, cooling ointment for softening a dry skin and when a mild antiphlogistic ointment is indicated.

9. *Foerster's Ointment*

Salicylic Acid 2.0 Gm.
Ammoniated Mercury Ointment q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Apply locally.
Indication: Antibacterial, keratoplastic.

10. *Astringent Ointment*

Bismuth Subgallate 3.0 Gm.
Zinc Oxide Ointment q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Apply locally.
Indication: Healing wounds.

11. *Mild Stimulating Ointment*

Ichthammol 4.0-8.0 Gm.
Zinc Oxide Ointment 30.0 Gm.
Misce et fiat unguentum.
Signa: Apply locally.
Indication: Subacute and chronic stages atopic dermatitis, acne, urticaria.

12. *Ointment to Hasten Suppuration*

Ichthammol
Rosin Cerate aa 15.0 Gm.
Misce.
Signa: Constant application.
Indication: For boils, abscesses.

13. *Drying Keratoplastic Ointment*

Acetpyrogall (N.N.R.)† 1.8 Gm.
Zinc Oxide Ointment 60.0 Gm.
Misce et fiat unguentum.
Signa: Local application.

*Precipitated sulfur is definitely less irritating to the skin of children than is sublimed sulfur.

*The writer has observed comparatively few instances of sensitivity to wool, including the wool fat incorporated in ointments, pastes, etc. This experience agrees with that of other pediatricians and dermatologists. Accordingly, the apprehension that exists among many clinicians regarding the use of wool fat in topical remedies among infants and children is, in the opinion of the writer, baselessly exaggerated.

†Ointment Lenigallol-Zinc is marketed by Bilhuber-Knoll in 15 Gm. tubes containing 6 per cent Lenigallol in zinc oxide ointment. U.S.P.

Indication: A favorite topical remedy for moist atopic dermatitis accompanied by itching.

14. *Cooling Ointments*

Zinc Oxide 20.0 Gm.
Calcium Hydroxide Solution 40.0 c.c.
Wool Fat
White Petrolatum aa q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Frequent applications.
Indication: An evaporating ointment for inflamed, dry skin.

(Lust-Levinsohn.)

15.

Aluminum Acetate Solution
Wool Fat aa 15.0 Gm.
Misce et fiat unguentum.
Signa: Apply freely.
Indication: An evaporating ointment for inflamed, dry skin.

(Lust-Levinsohn.)

16. *10-20-30 Paste (Burow's Paste)*

Aluminum Acetate Solution 10.0 c.c.
Anhydrous Lanolin 20.0 Gm.
Zinc Oxide Paste, N.F. 30.0 Gm.
Misce et fiat pasta.
Signa: Apply freely.
Indication: A mildly astringent paste that is useful in subacute dermatoses to absorb the residual exudate after most of the edema has been removed by means of wet dressings.

(This prescription is an example of a standard type of ointment base into which other medicaments may be incorporated. Antipruritic drugs such as ½ per cent phenol, 1/10 per cent menthol, 1 to 3 per cent Liquor Carbonis Detergens, 1 to 3 per cent ichthammol, etc., may be added. It is good strategy to reduce the quantity of the Burow's Solution to 5 c.c. instead of 10 c.c. in prescribing the above preparation for younger infants.)

17. *Astringent Ointment*

Lead Subacetate Solution 30.0 c.c.
Hydrous Wool Fat 10.0 Gm.
Benzoinated Lard 20.0 Gm.
Misce et fiat unguentum.
Signa: Apply freely.
Indication: Acute inflammatory dermatoses. (Lust-Levinsohn.)

18. *Antipsoriatic Ointment*

Pyrogallol 0.3 Gm.
Zinc Oxide Ointment 30.0 Gm.
Misce et fiat unguentum.
Signa: Apply freely
Indication: Powerful keratolytic in treatment of psoriasis, to be applied not oftener than once a day (frequent urinalyses). The strength of the ointment may be increased gradually to 5 per cent.

19. *Antipsoriatic-Parasiticidal Ointment*

Chrysarobin 0.1 Gm.
Petrolatum q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Apply cautiously (avoid region around eyes).
Indication: Psoriasis and parasitic infections.
Note: The strength of chrysarobin may be increased to 10 per cent (gradually). Avoid treating widespread areas at the same time. The urine must be examined regularly for albumin.

(Lust-Levinsohn.)

20. *Antiseborrheic Ointment*

Resorcinol 1.5 Gm.
Hydrous Wool Fat 4.0 Gm.
Petrolatum 30.0 Gm.
Misce et fiat unguentum.
Signa: Apply three times daily.
Indications: Antiseptic, keratolytic ointment for treatment of seborrheic dermatitis, atopic dermatitis, psoriasis, ringworm.

21. *Antiseptic-Keratolytic Ointment*

Rivanol* 1.5%
Salicylic Acid 3 %
Petrolatum q.s. ad 30.0 Gm.
Misce et fiat unguentum.
Signa: Constant application.
Indication: An excellent nonirritating antiseptic ointment for treatment of impetigo contagiosa.

(Hans H. Biberstein.)

22. *Zinc Bismuth Ointment (Neisser)*

Zinc Oxide
Bismuth Subnitrate aa 1.0 Gm.
Rose Water Ointment
Yellow Ointment aa 10.0 Gm.
Misce et fiat unguentum.

*Rivanol (Winthrop) is an acridine derivative. It occurs as a fine yellowish, crystalline powder. Chemically it consists of 2-ethyoxy-6,9-diamino-acridine lactate (ethodine). Rivanol in 1 to 2 per cent. in a zinc drying paint may also be used for the treatment of impetigo contagiosa.

Signa: Topical application.
Indication: Mild astringent.
(Lust-Levinsohn.)

23. *Vioform Ointment**
Iodochlorohydroxyquinoline, N.F. 3.0 Gm.
Petrolatum q.s. ad 100.0 Gm.
Misce et fiat unguentum.
Signa: Apply three times daily.
Indication: Chronic infections; dermatoses; atopic dermatitis, etc.

24. *Diodoquin Ointment*†
Diodoquin 3%-5%
Hydrophilic Base or Aquaphor 30 Gm.
Misce et fiat unguentum.
Signa: Apply several times daily.
Indications: Pyodermas, infected intertrigos, tinea cruris, atopic dermatitis and fissures, seborrheic dermatitis.
(Liefer and Steiner: J. Infest. Dermat. **12**: 203, 1949.)

25. *Cortisone Ointment*‡
Cortisone 0.3%
Aquaphor q.s.
Misce et fiat unguentum.
Signa: Apply locally.
Indication: Dermatitis herpetiformis.
(Ferguson, et al.: Arch. Dermat. & Syph. **651**: 535, 1952.)

26. *Antihistamine*§
Histadyl Cream (Lilly) 2% 30.0 Gm.
Signa: Apply.
Indication: Pruritic dermatoses (atopic dermatitis, etc.)
(Epstein and Macaulay: J. Invest. Dermat. **12**: 145, 1949.)

27. *Antihistamine* vel
Pyribenzamine Cream (Ciba) 2% 30.0 Gm.
Signa: Apply.
Indication: Antipruritic for dermatoses such as atopic dermatitis.
(Feinberg and Bernstein: J. A. M. A. **134**: 874, 1947.)

28. *Antihistamine*
Benadryl Cream (Parke, Davis)* 2% 30.0 Gm.
Signa: Apply by inunction.
Indication: Antihistaminic (pruritus, atopic dermatitis, urticaria, etc.).

29. *Merbromin and Salicylic Acid Ointment*
Salicylic Acid 1.5%
Merbromin 2.0%
Bentonite-Petrolatum Ointment Base 96.5%
Misce et fiat unguentum.
Signa: Spread lightly over the affected areas, cover it with a piece of gauze and keep it in place by means of a light bandage.
Indication: Atopic dermatitis with secondary infection.

30. *Hollander and McClenahan's Hydrophilic Ointment Base*
Petrolatum 32.0%
Bentonite 13.0%
Methylparaben 0.1%
Sodium Lauryl Sulfate 0.5%
Water 54.4%
Misce et fiat unguentum.
Signa: As directed.
Indication: Washable. An oil-in-water type of ointment base.
(Hollander and McClenahan: J. Invest. Dermat. **11**: 127, 1948.)

31. *Scabicticide*
Benzyl Benzoate 80 Gm.
Hydrous Wool Fat 25 Gm.
Glyceryl Monostearate 12 Gm.
Cellulose 9 Gm.
Water 165 Gm.
Triethanolamine 5 Gm.
Carbitol (ethyl diethylene glycol) 5 Gm.
Misce et fiat cremor.
Signa: After an initial hot bath using soap and water, the skin is dried well and the cream is rubbed all over the skin. After the cream dries, the patient must put on clean noninfested clothes.

*This cream is of the diadermic type.

*Vioform 3 per cent ointment (Ciba) is a brand of iodochlorohydroxyquinoline ointment.

†Diodoquin (Searle) is a 5,7-diiodo-8-hydroxyquinoline. It occurs as a fine pale yellow powder that contains 63.9 per cent of iodine. It is insoluble in water, dilute acids and alkalies, and is readily incorporated in ointments.

‡In a recent article (Goldman, L., and Trice, E. R.: Cortisone Acetate in Skin Diseases, Arch. Dermat. & Syph. **65**: 177, 1952) it has been stated: "Cortisone applied topically to the skin in ointment form in concentrations of 750 mg. per 30 Gm. of ointment produced no significant therapeutic responses in 114 patients, when the results were analyzed critically." The ointment bases were Aquaphor (an oxycholesterol-petrolatum ointment base), "Vanibase" (cetyl and stearyl alcohol, sodium lauryl sulfate, white wax and propylene glycol), "Mul-sol," polyethylene glycol (Carbowax) 1500, and zinc stearate.

§The effectiveness of antihistaminics in ointment bases is certainly questioned on the basis of the work done by Perry (Perry, D. J.: The Local Use of Benadryl Ointment. J. Invest. Dermat. **9**: 95, 1947).

Indication: Scabies.

(Goldman: A Cream Modification of the Benzyl Benzoate Treatment for Scabies, Arch. Dermat. & Syph. **39**: 878, 1939.)

32. *Podophyllin Ointment*

Podophyllum Resin (0.2%)
Carbowax 1500 30 Gm.
Misce.

Signa: Apply ointment twice daily. If inflammatory reaction follows, stop prescription and use wet compresses of boric acid or boric acid ointment.* For heavy crusting, discontinue the above prescription and apply a 2% salicylic acid in cottonseed oil under a cap. After the condition improves the ointment should be applied once daily.

Indication: Human type of tinea capitis.

(Reiss and Doherty: J. A. M. A. **147**: 225, 1951.)

33. *Salicylanilide Ointment*

Salicylanilide (5%)
Cationic Detergent (Hyamine 1622) 1%
Carbowax 1500 94%
Misce et fiat.

Signa: Apply twice daily.

Indication: Superficial mycosis (dermatophytosis) and tinea capitis (human and animal types).

(Schwartz, et al.: Indust. Med. **18**: 257, 1949.)

34. *Antibiotics*

Penicillin Calcium 50,000 units
Polyethylene Glycol (200) 25 Gm.
Carbowax (4000) 25 Gm.
Carbowax (1500) to make 100 Gm.
Misce et fiat unguentum.

Signa: Apply frequently.

Indication: Pyoderma, impetigo contagiosa, ecthyma.

(Macek, Gakenheimer, and Daughenbaugh: J. Invest. Dermat. **8**: 209, 1947.)

Aureomycin (2%) 0.6 Gm.
Qualatum (Almay) 30.0 Gm.
Misce et fiat unguentum.

Signa: Apply three times daily.

Indication: Prophylactic spread; lesions herpes simplex and in Kaposi's varicelliform eruption.

(Baer and Miller: J. Invest. Dermat. **13**: 5, 1949.)

Aureomycin Hydrochloride (3%)
Lanolin
Mineral Oil
Petrolatum aa 30 Gm.
Misce et fiat unguentum.

Signa: Apply.

Indication: Superficial pyodermas; impetigo contagiosa and ecthyma.

(Sawicky, et al.: J. Invest. Dermat. **15**: 339, 1950.)

Tyrothricin Cream (0.05%) 30 Gm.
(Smith Dorsey Co.)

Signa: Apply.

Indication: Antibacterial against gram-positive pathogens.

Tyrothricin Concentrate 1.0 Gm.
Carbowax 1500 q.s. ad 30.0 Gm.
Misce et fiat unguentum.

Signa: Apply.

Indication: Impetigo contagiosa and eczematoid dermatitis.

Calcium Penicillin (1,000 Oxford units per gram)
Hydrous Wool Fat
White Petrolatum aa 30 Gm.
Misce et fiat unguentum.

Signa: Apply liberally three times daily or apply upon a dressing and change twice daily. (Keep ointment refrigerated.)

Indication: Pyoderma, impetigo contagiosa, and ecthyma.

*Wet dressings of Matricaria (German chamomile) may be used instead of boric acid for children in order to avoid the possible danger of boric acid absorption. (Author's note.)

Medical Progress

ACUTE RESPIRATORY DISEASE WITH SPECIAL REFERENCE TO PATHOGENESIS, CLASSIFICATION, AND DIAGNOSIS

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DES MOINES, IOWA

INTRODUCTION

IT IS the purpose of this paper to review the literature on acute respiratory infections involving the larynx, tracheobronchial tree, and lung parenchyma. A classification of these infections is presented; the pathogenesis of their signs and symptoms and diagnostic criteria is discussed.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The anatomy of the lung has been fully described in Miller's classic monograph on the subject. Of especial interest here is the fact that the terminal bronchioles have a mean diameter of 0.192 mm. Because of the lobular structure of the lung, inflammatory swelling of the epithelium may therefore prevent ventilation of relatively large amounts of lung parenchyma.[1]

In 1941, Robertson[2] reviewed the literature pertaining to phagocytosis of foreign material in the lung and discussed the resistance of the lungs to infectious material. Twenty years previously, Jackson[3] emphasized that of all the defense mechanisms of the respiratory tract the tussive blast was pre-eminent. Others have more recently discussed these mechanisms.[4] For detailed discussion of these aspects of respiratory disease, the reader is referred to these sources.

From The Raymond Blank Memorial Hospital for Children.

CLASSIFICATION OF ACUTE RESPIRATORY DISEASE

The following classification of respiratory infections is employed in this review. Its basis is the anatomic situation of the disease, which may be determined in the case of each entity discussed by adequate history and physical examination. The writer considers the etiologies of respiratory disease are too varied and mixed to make them amenable to etiological classification from a practical, clinical point of view.

1. Infections of the larynx:
   a. Acute laryngitis.
   b. Acute spasmodic laryngitis.
2. Infections of the tracheobronchial tree:
   a. Acute tracheitis.
   b. Acute tracheobronchitis.
   c. Acute laryngotracheobronchitis.
   d. Foreign bodies.
   e. Acute bronchitis.
3. Influenza and grippelike infections.
4. The pneumonias:
   a. Bacterial pneumonias:
      (1) Lobar pneumonia.
      (2) Bronchopneumonia (lobular).
   b. Pneumonias of mixed etiology (atypical pneumonias).
   c. Bronchiolitis (acute interstitial pneumonitis of infants).

THE LARYNX

In the adult, laryngeal inflammations may occur incident to acute respiratory infections but seldom produce much symptomatology other than hoarseness, pain, etc. In the child, however, the situation is quite different and certain important and

often very acute situations may arise. This is due almost entirely to the consistency, proportions, and dimensions of the larynx in children. The larynx of children is composed of softer tissues. The cartilaginous supporting elements contain less calcium and are less rigid. Connective tissues are less dense and with inflammation tend to become more edematous. As the child's neck is shorter, relatively, than the adult's so also is the relative distance from the base of the tongue to the inferior border of the cricoid cartilage. The point in the larynx at which inflammatory edema is most likely to produce acute obstruction is bounded anteriorly by the epiglottis and epiglottic tubercle, laterally by the aryepiglottic folds and vocal cords below, and posteriorly by the mucosa which closes the larynx behind and is characterized by its loose attachment to adjacent structures and is normally capable of some free movement. Add to this anatomic situation the laryngeal muscle spasm which Jackson believes plays such a role in childhood croup, and it is readily seen why children may suffer acute respiratory distress so quickly during episodes of respiratory infections.

Two laryngeal conditions are of interest here in the consideration of acute respiratory infections: acute laryngitis and acute spasmodic laryngitis. Although acute laryngotracheobronchitis involves the larynx, it is considered under the section of the tracheobronchial tree, since the major pathology lies there rather than in the larynx.

Acute laryngitis usually occurs as a part or consequence of an upper respiratory infection. It represents the first phase of the tendency for respiratory infections to progress downward. This tendency is opposed by the resistance of the patient.[5] In addition, the larynx is often bathed in infected secretions dropping down from the infected nasopharynx. These secretions contain flora usually found associated with upper respiratory infections: streptococci, staphylococci, *Neisseria catarrhalis*, the pneumococcus, *Hemophilus influenzae*, diphtheroids, etc. They also contain various viruses known to cause upper respiratory infections. Rabe[6] believes that viral agents and type B *Hemophilus influenzae* are predominant etiological agents. Whatever the etiology, varying degrees of acute inflammation of the larynx occur. Tissues become edematous and infiltrated with polymorphonuclear leukocytes. Subglottic tissues may become mounded up by the reaction to infection. Secretions of mucoid, to frankly purulent nature, may be found on laryngoscopic examination. Characteristically, they wipe away, leaving a clean but red and inflamed mucosa on laryngoscopy. In addition to the constitutional symptoms one expects with such an infection, diagnostic localizing signs are present. These include the familiar initially dry, harsh "barking" cough of nonproductive nature, yielding gradually to a looser cough, more productive in character. Depending on the degree of inflammation present, voice changes varying from hoarseness to aphonia may be noted. This sign arises as a result of inflammatory thickening and deformity of the vocal cords. Edema may be sufficient to embarrass the patient's airway. Laryngeal stridor is due to impingement on the airway by

inflamed laryngeal structures. It is at first inspiratory in time because of the tendency for the larynx and tracheobronchial tree to become increased in length and decreased in diameter with inspiration. In severe cases the stridor may be two-way: inspiratory and expiratory. In contradistinction to acute spasmodic laryngitis, the dyspnea of acute laryngitis is of more gradual onset. Dyspnea may be so severe as to produce cyanosis. When acute laryngitis is of this severity, it represents the first stage of acute laryngotracheobronchitis. In the child who presents with laryngeal signs, a number of conditions must be ruled out before the diagnosis of acute laryngitis can be made with certainty. Jackson mentions in particular the following: laryngeal foreign body, loose or fixed foreign body in the trachea, and aspiration of material regurgitated from the esophagus due to an obstructing lesion. It must be remembered that laryngeal signs may persist after a foreign body has been coughed up, and that the presence of a foreign body may produce a sick, febrile child, although usually signs of an upper respiratory infection are lacking. More commonly, however, one must rule out diphtheria, pertussis, and a tracheobronchial component to the condition. Strictly speaking, it is impossible to rule out diphtheria except by laryngoscopic and bacteriologic studies. Because of the widespread use of diphtheria toxoid today, these studies are done in practice far less frequently than recommended by writers as little as fifteen years ago.

Acute spasmodic laryngitis, spasmodic croup, or croup diathesis is a most interesting condition. Its characteristically sudden onset, usually at night, is well known. It is associated with either an upper respiratory infection or previously evident acute laryngitis of variable degree. Jackson suggests that this condition, in which the degree of laryngospasm is out of proportion to the catarrhal inflammation present, arises in the recumbent or sleeping child because pharyngeal secretions are aspirated. Due to the normal protective reflex mechanism spasm of the glottis occurs, together with sudden inspiratory efforts. In severe cases not only glottic spasm is seen but sphincteric closure of the larynx as well. Laryngospasm, continued attempts to inspire air, and pharyngeal secretions, together with emotional tension, all combine to perpetuate a vicious cycle. On laryngoscopic examination such patients are found to have a mucosa which is lavender or violet in color, but otherwise normal. This is a product of the tremendous spasm and vascular engorgement which have occurred. Jackson notes that the mucosa returns to more or less normal appearance when a laryngoscope is inserted because the vicious cycle noted above is broken by providing the patient with an adequate airway.[7]

The cervical, supraclavicular, and substernal retraction signs which one sees with obstructing lesions of the larynx are due to the fact that, with attempted inspiration, intrapulmonic pressure is reduced below atmospheric pressure and depression of the areas abutting on the thoracic cage occurs, as these have the least skeletal support. Laryngeal stridor may be transmitted down the tracheobronchial tree and heard on auscultation of the chest.

It is distinguished from wheezes within the chest by following it to its source with the stethoscope bell.

THE TRACHEOBRONCHIAL TREE

Infections of the tracheobronchial tree may be classified according to the portion of tract involved clinically. Utilizing certain signs and symptoms, one may make a clinical diagnosis of any of the following entities: acute tracheitis, acute tracheobronchitis, acute laryngotracheobronchitis, and acute bronchitis. While in adults many reports record various proportions of the flora noted above as usually associated with acute respiratory infections, Jackson[7] in 1936 felt that in children these inflammations are caused by streptococci in about 90 per cent of cases, *H. influenzae* in about 3 to 5 per cent of cases, and the pneumococcus and mixed infections in the remainder. In 1948, however, Rabe, in his series on infectious croup, reports 7 per cent of diphtheritic origin, 9 per cent due to type B *H. influenzae,* and 84 per cent of presumably viral etiology.

The pathologic picture produced in the tracheobronchial tree is widely variable in degree but is essentially that of an acute infection. Edema, exudation, and polymorphonuclear infiltration are present to a variable degree. In some instances only catarrhal inflammation of the tracheobronchial tree was seen on bronchoscopy and smears of bronchial secretions revealed mainly neutrophils, some lymphocytes, a few monocytes, and a fair to considerable amount of epithelial cells and cellular debris.[8] Other observers have reported the presence of tracheobronchitis with necrotizing desquamation of respiratory epithelium.[9] The pathologic picture of acute laryngotracheobronchitis probably represents the extreme in acute inflammation of the lower respiratory tract. Microscopically, the picture is that of any pyogenic inflammation. In this condition the exudative phase of inflammation is most marked but the full extent of the pathology is best appreciated with the bronchoscope. The mucosa is deep red in color, subepiglottic tissues are mounded up, and secretions wipe away cleanly, leaving no erosion or ulceration. Initially the secretions are mucoid, later become purulent, thick, tenacious, and difficult to expectorate. Some bronchial orifices are filled with pus, others are covered with crusts having the appearance of dried serum containing a little pus. Bronchial secretions are often dried and gumlike. Rarely the tracheobronchial mucosa may be seen to present a dry, even glazed appearance.[7]

Acute tracheitis, according to Scadding, may be diagnosed in the patient with respiratory infection who has a cough, usually nonproductive at first and later becoming productive, and who has retrosternal discomfort or pain. Patients with this condition usually have, also, general malaise, generally no fever, or at most a low-grade fever, and a white blood count of 11,000 to 20,000. Sputum usually contains hemolytic streptococci, *Streptococcus viridans* and *Hemophilus influenzae.*[9] This reviewer was unable to find in the literature any definitive explanation of the origin of retrosternal pain but it is probably to be found in the common observation at bronchoscopy that the carina is an especially sensitive structure and often requires additional anesthesia. In

addition, this area of the tract has been found to be inflamed at bronchoscopy in patients who complained of retrosternal pain.[8]

Acute tracheobronchitis is an entity which Kornblum and Reimann[10] think should be recognized for they feel that it separates, so to speak, an upper respiratory infection from a parenchymal infiltration of the lungs. In their radiologic study of eighty-six patients with severe upper respiratory infections, they classified forty as radiologically negative, twenty-four as having acute tracheobronchitis, and twenty-two as having so-called atypical pneumonia, which will be discussed later. They acknowledged that only bronchial lesions are seen by x-ray, but state that bronchoscopy has firmly established the tracheal element of the disease. Radiologic recognition of this entity was made on the basis of increased prominence of hilar markings. Since acute inflammation of the bronchi, if of sufficient degree, extends into the peribronchial supporting structures and also because bronchial inflammation produces peribronchial lymphatic engorgement, it is reasonable to suppose that the increased bronchial markings seen on the radiogram in this disease are due to the increased tissue density produced by these two components of bronchial infection. It is axiomatic that on a normal x-ray film, excluding structures rich in mineral content, such as bone, the tissues which cast the densest shadow are those containing the most water. Inflamed tissues contain more water than usual in the form of edema fluid and therefore cast a heavier shadow. Physical signs in this condition found in the chest are coarse râles and occasional dullness, but the distinguishing feature is that they are of constantly shifting nature, invariably changed when the patient coughs. These are due to the shifting of bronchial secretions.[2, 10, 13]

Acute laryngotracheobronchitis is the most serious infection involving the tracheobronchial tree. Chevalier Jackon stated it is a definite entity because of its definite clinical characteristics rather than merely a more severe than usual form of respiratory disease of the winter months. Certainly when one considers the potential effects of this condition on the child, its place as an important clinical entity cannot be questioned. The patient with this disease presents the appearance of acute illness due to the absorption of bacterial products, and the magnitude of the infection within the respiratory tract. Fever may reach 105° F. and varying degrees of hoarseness are present. Dyspnea is early a prominent part of the picture, is at first inspiratory, later biphasic, and is the product of inflammatory and especially exudative impingement on the airway. The accessory muscles of respiration are used, and an audible wheeze may often be heard at the patient's open mouth. Initially pallor is noted due to the intense effort the patient must exert to ventilate and the fatigue inherent to the effort. Later, as the airway becomes more impaired, anoxic anoxia occurs, the amount of reduced hemoglobin in the blood increases, and cyanosis is seen. Usually patients in this stage of the disease have what is described as an ashen color. From the time dyspnea is first evident, signs of air hunger are usually present as apathy, restlessness, and easy fatigability. Cough is

commonly croupy from the onset but may be modified later by the abundant secretions in the tract. Secretions shift with activity and cough of the patient and so physical findings in the chest are constantly variable. Rhonchi, coarse râles, and areas of shifting dullness may be found. When persistent areas of dullness are found in patients with this disease, together with absent or diminished breath sounds and an increased respiratory rate, the probability is that these are areas of atelectasis produced by obstructing secretions rather than consolidated areas of bronchopneumonia, which is an uncommon complication of the disease. Indeed, before the era of antibiotics repeated bouts of segmental or lobar atelectasis was the natural course of the disease for which the only treatment then available was repeated aspiration of the tracheobronchial tree by appropriate means. This meant the employment of the laryngoscope, the bronchoscope, or tracheotomy. Jackson stated that if the airway is preserved and atelectasis prevented, the disease is pretty much self-limited.[7, 11]

Foreign Bodies.—Of particular pediatric interest in the differential diagnosis of laryngotracheobronchial disease is the matter of excluding diphtheria and the presence of a foreign body. Diphtheria may be ruled out by a history of immunization, laryngoscopic examination, and bacteriologic studies of secretions. Jackson suggests giving antitoxin in doubtful cases and that if the disease is of diphtheritic origin, prompt improvement is obtained while none occurs if the disease is nondiphtheritic.

The presence of a foreign body in the trachea may be suspected in the patient who presents with symptoms referable to the trachea, such as cough, hemoptysis, wheezing, or dyspnea, if the following special signs are noted: a palpatory thud over the anterior upper chest, the audible slap and asthmatoid wheeze heard by placing the stethoscope bell at the patient's open mouth. The palpatory thud represents the blow of a foreign body as it strikes the tracheal walls with respiration. The audible slap is the auscultatory component of the same phenomenon. The asthmatoid wheeze represents the sound created by air rushing past the foreign body as it lies in the trachea and is usually expiratory in time.

Bronchial foreign bodies may produce any of the symptoms and signs noted above. Of particular interest is their tendency to sometimes remain asymptomatic for some time and then produce symptoms at a later date. Characteristically, vegetal foreign bodies produce immediate laryngotracheobronchitis, coughing bouts, irregular fever, and a systemic reaction whose severity is in inverse proportion to the age of the child. When a foreign body in a bronchus, due either to partial obturation or because of the inflammatory reaction its presence produces, causes a partial obstruction, the physical signs produced in the chest are variable in nature from time to time. The most constant finding is the presence of râles on the involved side distal to the obstruction, which are due to increased bronchial secretions.

Where a foreign body produces complete obstruction in a bronchus, physical signs are replete. Limited expansion of the affected part of the chest occurs because of lack of ven-

tilation of the segments of lung within. Tactile fremitus is decreased or absent because the part of the bronchial tree down whose passages such sounds normally reverberate is plugged. Decreased resonance is ordinarily seen and is caused by the resorption of gases within the nonventilated lung segments. However, tympany may be present for a long time after the onset of obstruction, in which case râles are heard on the *uninvolved* side.

When a foreign body case is seen early, pneumonia may be suspected. However, the diminished tactile fremitus, decreased breath sounds, and absence of tubular breathing should soon exclude this diagnosis. "Bronchial obstruction in pneumonia is extremely rare."[2] In doubtful cases the fluoroscope and x-ray may resolve the problem by revealing the mediastinal shift and modified diaphragmatic excursion characteristic of bronchial obstruction.

Acute bronchitis is an infection of the bronchi which may occur as a primary disease, as a component of acute tracheobronchitis or laryngotracheobronchitis, or secondary to the common upper respiratory infections. In the sense that it is used here, the condition as a part of acute laryngotracheobronchitis of children is excluded. If one accepts the concept of Kornblum and Reimann, bronchitis rarely occurs as an isolated entity, anatomically speaking, but more usually as a part of a more extensive inflammation involving the trachea as well.[10] Certainly the bronchoscopic studies of the Commission for the Investigation of Acute Respiratory Diseases established by the Army during World War II have demonstrated there is also an almost invariable tracheal phase to the disease. Bacteriologic studies by this commission have been published in voluminous tabular form. The following organisms have been isolated from sputum and bronchial washings from cases studied:

1. α, β, and γ streptococci, *Staphylococcus albus,* typable pneumococci and *Hemophilus influenzae* as the predominant organisms.

2. *Hemophilus hemolyticus,* coliforms, *Klebsiella pneumoniae,* and diphtheroids in a small number of cultures.[8]

The pathologic picture in acute bronchitis has been discussed, but because of the small diameter of the bronchial part of the tracheobronchial tree, bronchial involvement gives rise to certain physical signs which enable one to make a positive diagnosis although bronchitis may merge imperceptibly into bronchopneumonia. This again is an example of the tendency of respiratory infections to descend the lower respiratory tract. In addition to the constitutional signs of infection such as malaise, fever, etc., low substernal pain and cough may be noted. Substernal pain is probably a product of carinal inflammation, the afferent limb of the cough reflex apparently being subserved by nerve fibers which have been found to penetrate as far distally as the alveoli. It is generally accepted that no areas of dullness are found in bronchitis. Where large bronchi are involved, rhonchi and coarse râles are heard. Where the smaller bronchi are infected, the râles heard are of finer quality. As the disease progresses and secretions become less viscid, the râles may be-

come moist or bubbling in character. The râle has been euphoniously defined as, "The snick of a bubble bursting." However, the character of râles is a function of the diameter of the bronchus, the viscosity of the secretions, the amount of secretions in the bronchus, and the depth and vigor of respiration. Reduction of bronchial diameter by edema or secretions may produce poor ventilation leading to cyanosis and an expiratory wheeze. Usually acute bronchitis is bilateral, though segmental disease may be seen and probably represents areas of bronchopneumonia.[12]

Acute bronchitis may progress to two different types of pneumonia from which it is not easily distinguished during the early phases of this progression. Infection may extend distally in bronchioles to the alveoli and produce an exudative, consolidating intra-alveolar pneumonia of lobular distribution, which histologically is seen to pass through the stages of hepatization and resolution much as its lobar counterpart does. Second, infection may spread outward from the bronchi into the peribronchial stromal elements, thence into the interalveolar septa to produce the histologic picture of an interstitial pneumonia.[14, 15] While the significance of these two routes of extension of bronchitis is discussed in the section on the pneumonias, the clinician must remember that microscopic evidence of lobular or bronchopneumonia may exist before the usually anticipated signs of areas of dullness and tubular breath sounds are present. The ability of the clinician to distinguish between an acute bronchitis and an early bronchopneumonia therefore depends largely on the size and number of lung lobules involved, that is, the parenchymal areas of consolidation or interstitial pneumonia must be large enough to be detected by physical examination. Finally, it must be noted that, where bronchial infection is a virulent one, both children and adults may be prostrate with their disease and show complete absence of any signs of pneumonia by either physical or radiologic examination.

GRIPPE AND INFLUENZA

Included here are several poorly demarcated infectious respiratory syndromes of man, each one no great threat to life yet predisposing the patient to potentially serious secondary bacterial infection. Together the annual cost to the public health and working time is tremendous. The literature on the subject is in a state of confusion and certainly some of this is due to the multiplicity of nomenclature and diagnostic criteria. In 1935, two years following the isolation of the Influenza virus, Francis[16] characterized "influenza" as having ". . . sudden onset with constitutional symptoms, chilliness, fever, myalgia, headache, mild respiratory symptoms with coryza, the presence of leukopenia, and a course of two or three days which was followed by considerable asthenia and exhaustion." In 1939, Andrews[17] stated, "It must be emphasized that we do not yet know enough to diagnose individual cases 'epidemic influenza' or as 'febrile catarrh' on purely clinical grounds." In 1944, the Army Commission for the Investigation of Respiratory Disease[8] coined the phrase "acute undifferentiated respiratory disease" and included in this category cases diag-

nosed by medical officers as nasopharyngitis, bronchitis, grippe, and common cold. In a study of 1,667 cases of acute upper respiratory infections studied at a university infirmary, the following clinical picture is noted: fever for one day or more, chills, aches and pains, sore throat, laryngitis, tonsillitis, cervical adenitis, occasional bronchitis, rarely splenomegaly, and a leukocytosis of as much as 30,000, contrary to the usually accepted opinion of leukopenia in the so-called "grippe."[18] Despite the confusing descriptive literature concerning these conditions, they are familiar to every practitioner.

Epidemic influenza is the one infection in this group which can be dignified with a diagnosis amenable to laboratory proof and etiological classification. The clinical picture is quite indistinguishable from that noted above; however, the disease is said to occur periodically in epidemic form. Public health studies of the disease are exhaustive yet contribute little to the clinical problem it presents. Isolated cases are not discussed in current texts. Proof of diagnosis of influenza depends on the isolation and identification of the causative virus and demonstration of a rise in titer of specific antibody in the circulating blood. It is a rare clinical laboratory which is equipped to perform such procedures. A more practical presumptive proof of diagnosis is found in the Hirst reaction based on the fact that the serum of people with significant specific antibody titers will agglutinate the red blood cells of certain other species.

Until such time as virologists learn more about viruses in general and make available to clinical workers techniques by which etiological agents can be conveniently and consistently identified, it is likely that the present state of confusion concerning these entities will remain. The syndromes they produce are so similar as to preclude clinical differentiation. In addition to the complex technical problems involved, this problem is made infinitely more difficult by the variety of virus strain differences, the inherent biologic instability of viruses, the existence of antigenically weak strains, the fact that clinical infections are of short duration and weak titers in the patient are inevitable, the possibility that both apparently healthy men and experimental animals may harbor the strains under study, and the nonspecific tissue reaction evoked by known viruses. Finally there exists the problem of determining to what extent viral-bacterial synergism acts in producing the various syndromes of respiratory disease.[19] Some discussion of this subject as it pertains to parenchymal lung infections will be found in the section on pneumonias.

THE PNEUMONIAS

Pneumonia is defined as, "Inflammation of the lung; pneumonitis. Used without qualification the term implies lobar pneumonia."[20] Anderson[21] states, "Inflammation of lung tissue when unaccompanied by necrosis is called pneumonia, though sometimes it is quite logically referred to as pneumonitis." Pneumonia is a disease whose outward clinical picture was well known to the ancients. It is described by Hippocrates, and Aeretaeus the Cappadocian especially well described the course leading to death. Aeretaeus also described

pleurisy and its pathogenesis. Physical findings were not recorded until 1761 when Leopold Auenbrugger noted impaired resonance on percussion in a patient who presented the outward picture of pneumonia. He also noted venous distention on the affected side as well as decreased respiratory excursion. In 1830, Laennec published his classic *Treatise on the Diseases of the Chest and on Mediate Auscultation* in which he established auscultation as a part of physical examination, described the course of physical findings in the chest in lobar pneumonia, and explained the pathogenesis of these signs.[22]

Lobar Pneumonia.—Lobar pneumonia ordinarily is caused by the pneumococcus when it is aspirated into the alveoli in such numbers as to exceed the resistance of the patient. Rarely Friedländer's bacillus or streptococci may produce pneumonia of lobar distribution. Following the description of Laennec, it is customary to divide the natural course of the disease into four stages each with its characteristic pathologic picture; the stage of inflammatory edema, red hepatization, gray hepatization, and resolution.[23]

The pathogenesis of many features of the clinical picture of lobar pneumonia may be explained on the basis of altered physiology. In addition to the patient looking febrile and *sick,* a systemic manifestation of the infection, the presence of expiratory grunt, together with dilatation of the alae nasae and cyanosis disappearing as consolidation progresses, is commonly seen as part of the typical picture of onset. Probably the early presence of cyanosis is due to the fact that in the stages of exudation and early hepatization, circulation of blood still takes place through the involved portion of lung tissue. Such blood as passes through these areas is not oxygenated due to the presence of alveolar exudates and so hemoglobin remains in reduced form. Thus there is built up in the patient's blood stream an increasing amount of reduced hemoglobin until the level is reached at which cyanosis occurs. Because, as consolidation progresses, thrombosis of small pulmonary vessels occurs, the flow of blood through consolidated parts of the lung incapable of oxygenating it is progressively diminished. Eventually only a minimal amount of the blood contains reduced hemoglobin and the patient's cyanosis disappears though his lung may show much consolidation and his disease has actually progressed. By the same token, one may theorize that the labored respiration has its origin in the increased reduced hemoglobin in the blood stream implying a decreased oxygen tension stimulating the respiratory center via receptors in the aortic arch and carotid body. The absence of appreciable reduced hemoglobin in the patient whose involved lobe is completely consolidated probably accounts for relative lack of respiratory distress in such patients.

During the period when x-ray was first used for the study of chest disease, there was considerable discussion as to whether lobar pneumonia began at the hilus and spread peripherally or conversely. Some have felt the disease always began at the hilus in children and at the periphery of the involved lung segment in the adult.[24] Others have stated with great conviction that every lobar

pneumonia in children begins at the pleural surface and progresses medially.[25] Over the course of years it has become apparent that both forms of lobar pneumococcal pneumonia occur. More frequently one sees the first sign of consolidation by x-ray in the subpleural parenchyma. However, appreciable numbers of pneumonias of central origin are seen. Where obvious pneumonia in the absence of typical signs is seen, often there will be found on x-ray a layer of uninvolved parenchyma just lateral to the area of consolidation and many feel this is the reason for the absence of physical signs.[24] Some have stated that pneumonias of central origin are cases of "atypical pneumonia," i.e., of presumably viral etiology while pneumonias of peripheral origin are always of pneumococcal etiology.[13, 26] Despite divergent opinion regarding interpretation of the radiographic picture, x-ray findings must be correlated with the other clinical findings to be of value in the management of any given case. X-ray is of value early in the course of disease, for bacterial pneumonias usually give positive radiologic signs six hours after the onset of the disease and in practically all cases twelve hours after the onset of the infection.[27]

Bronchopneumonia.—Logically this condition should be called lobular pneumonia if one is to be consistent with the term lobar pneumonia. Except for the fact that primary bacterial pneumonias in young children are usually of lobular distribution, most bronchopneumonia is secondary to infection higher in the tracheobronchial tree. In adults it usually represents the end point in the tendency of respiratory disease to descend the tract. This is evident in the usual lower lobe distribution of the disease in the lung at post mortem or in the chest film of the patient. Scattered areas of consolidation of lobular distribution, often with necrosis and ulceration, are seen. Microscopically, the alveolar exudate in these foci is seen to consist of little fibrin, in contrast to pneumococcal infection, and mostly erythrocytes, and neutrophils in plasma. The lobular distribution of this disease is seen in the chest film as the typical "bunch of grapes" appearance of consolidated areas.[26]

Bronchopneumonias are said to arise from bronchial infections by two different routes, which probably may occur simultaneously. Foci may arise by extension of bronchial and bronchiolar infection deep into the lung stroma and alveolar septa and this has given rise to calling some bronchopneumonias "interstitial" in nature.[13, 23] Second, foci may arise by extension distally in the bronchioles and into the alveoli to produce the patchy involvement characteristic of the disease.[26]

Because, in adults and to a degree in children, this type of pneumonia is usually secondary, the organisms which are etiological factors are many and often several are present in any one case. Streptococci, staphylococci, pneumococci, and *Hemophilus influenzae* are the most frequent organisms seen in the disease. The presence of typable pneumococci in the pharynx or sputum of a young child does not in any way demonstrate that the child has a pneumococcal bronchopneumonia.

"The recognition depends more on general manifestations than on physical examination of the lungs for often small patches exist without characteristic signs of consolidation."[12] In infants death may occur before physical findings appear in the chest. Fine, medium, and moist râles of variable distribution are heard but these may often be masked by the coarse râles of a pre-existing bronchitis. The presence of signs of consolidation depends entirely on the size and distribution of confluent foci in the lungs. The physical signs in the bronchopneumonia patient vary from day to day and usually with the patient's cough.[12] Rarely, it may happen that a bronchopneumonia becomes sufficiently extensive and confluent to produce dullness and tubular breath sounds over most of a lobe, presenting a picture indistinguishable from lobar pneumonia on the basis of physical findings. It may be differentiated by the difference in prodrome compared with ordinary lobar pneumonia.

Mixed Pneumonias.—In this category, the reviewer has placed those acute inflammations of lung parenchyma which are of uncertain etiology and of variable clinical course. They are probably best known as "primary atypical pneumonias" which is a poor term since they are rarely if ever primary, and the use of the adjective "atypical" seems to be based on the misconception that naming something is equivalent to saying something about it. Certain it is, however, that most observers are agreed that these inflammations are pneumonias in the pathologic sense of the word. In the matter of nomenclature, Plummer and Ensworth[28] have published a list of names which have been applied to such an infection:

1. Virus pneumonia
2. Virus type pneumonia
3. Primary virus pneumonitis
4. Interstitial virus pneumonia
5. Interstitial virus pneumonitis
6. Acute interstitial pneumonia (pneumonitis)
7. Acute interstitial pneumonitis
8. Pneumonitis
9. Acute pneumonitis
10. Simple pneumonitis
11. Atypical pneumonia
12. Primary atypical pneumonia
13. Atypical pneumonitis
14. Atypical pneumonia with leukopenia
15. Atypical bronchopneumonia of unknown etiology
16. Bronchopneumonia in adolescence
17. Bronchopneumonia of unknown etiology
18. Bronchopneumonia of unknown etiology (variety X)
19. Acute influenzal pneumonitis
20. Acute influenzal pneumonia
21. Disseminated focal pneumonia
22. Benign bronchopulmonary inflammation associated with transient radiographic shadows.

To the above list, this reviewer would add what he considers the monster of them all, "typical atypical pneumonia." In 1942, Dingle and Finland[29] stated that, "Characterization of the condition is difficult and probably will remain so until the etiological problem is solved." Kornblum and Reimann[10] feel that, "The term pneumonitis has come to be used rather loosely and at times one does not know precisely what is meant. The term pneumonitis is often employed in the presence of a small pulmonary opacity which is believed to be rather benign in character in order to differentiate from the more

serious types of pneumonia. This use, of course, is not justifiable since the term pneumonia and pneumonitis are synonymous, having no reference to the severity of the lesion."

These infections are said by Reimann to have risen from obscurity because of: (1) antibiotic control of bacterial infection, (2) their establishment in the literature as entities, (3) more frequent use of x-ray, and (4) the increased incidence in troops in World War II. He expresses doubt that the incidence of such infections has actually risen. The apparent rise results from awareness of the disease after its delineation in 1938, greater general clinical interest in it, greater interest in etiological diagnoses, and the increased use of diagnostic x-ray.[30] In 1949, Verco[31] observed that the character of pneumonias in the preceding decade had greatly changed. He felt the general success of chemotherapy had thrown into sharp relief pneumonias not affected by it and expressed the opinion that few were bacterial in nature, and that most were of a heterogenous type called atypical pneumonia.

Undeniably these so-called atypical pneumonias are an integral part of acute respiratory infections. As seen in Fig. 1, they have lately enjoyed a certain vogue in the literature. A review of articles published to the present (1953) seems to indicate that they are caused by the synergistic effect of various bacteria which normally inhabit the *upper* respiratory tract together with many different viruses poorly known at present. Because of the variable bacterial and viral situation seen in cases reported, it appears that these two types of disease-producing agents may, in infinitely variable admixture, produce markedly variable syndromes. It is for this reason that the writer refers to them as the "mixed pneumonias."

Historically, the condition is not a new one, having been recognized clinically as long ago as 1872.[29] In 1917, there was a report of respiratory disease in a command of the British Army in which a typical case of what is termed "purulent bronchitis" is

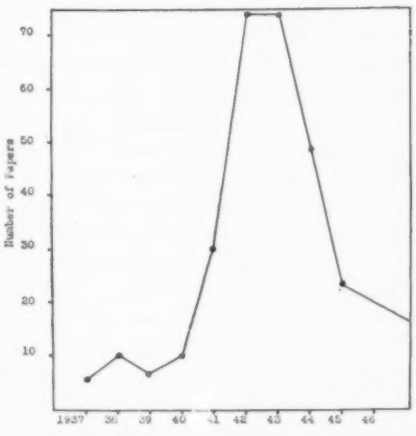

Fig. 1.—Graph showing number of papers on "atypical pneumonia" published each year from 1937 to 1945. (After Reimann, 1947.)

described and the picture is identical with what the pediatrician today terms "bronchiolitis."[32] About 1930, European groups reported shadows in chest films interpreted as localized consolidations though the patients had none of the symptoms associated with acute pneumonia. This was noted in instances of epidemic respiratory infections and in patients in tuberculosis clinics with upper respiratory infections.[33] In 1939, Smiley[34] offered his classification of respiratory disease and placed in a

separate category those infections in which there were x-ray densities in the lung fields in the absence of physical signs. He termed this situation acute interstitial pneumonitis and suggested that all patients with upper respiratory infections and temperatures above 102° F. have chest films taken so the diagnosis might be more frequently established.

The clinical picture is characterized chiefly by its great variability. In general, however, there is almost always a prodromal upper respiratory infection. The onset is not as severe as that seen in lobar pneumonia, and consists of chills, fever, chest pain, paroxysmal often productive cough, and rather profound general malaise. Râles of variable distribution are heard together with wheezes. Signs of frank consolidation are usually absent. Localization of physical signs is usually confirmed by x-ray.[35, 36, 37] Reimann, in his excellent review of the subject in 1947, tabulates the incidence of symptoms and physical signs in reported series. Computation of these figures reveals their incidence to be about as follows, expressed in terms of percentage of patients showing a symptom or sign in reference to the total number of cases reviewed:

Symptoms (Per cent)

1. Cough	84	12. Sweating	29
2. Malaise	66	13. Nausea	15
3. Headache	60	14. Hemoptysis	13
4. Sputum	57	15. Rigor	12
5. Gradual onset	56	16. Vomiting	12
		17. Dyspnea	10
6. Chills	50	18. Dizziness	7
7. Myalgia	40	19. Epistaxis	5
8. Anorexia	37	20. Duration of fever 4 to 9 days in	70%
9. Chest pain	35		
10. Coryza	34		
11. Sore throat	33		

Physical Signs (Per cent)

1. Fever	82	6. Conjunctivitis	20
2. Râles	72		
3. Pharyngitis	64	7. Pleural rub	7
4. Dullness	58	8. Cyanosis	5
5. Lymphadenitis	25	9. Meningismus	3

Chest films of patients with this condition show infiltrations of many types which have been classified as:

1. Increased hilar shadows, mild to severe in degree.
2. Lobar distribution, of a texture suggesting ordinary bronchopneumonia.
3. Hilar infiltrations, extending to involve a whole lobe.
4. Scattered miliary densities.

Curtzweiler and Moore[39] note that many cases would not be recognized if x-rays were not taken. They feel that most "central pneumonias" actually involve the bronchus dorsalis and emphasize the need for lateral views. Unfortunately, in most of the reported cases of mixed pneumonia no lateral views were taken.[40] The radiographic densities seen in lung fields in these cases are in no way diagnostic, however, and the observation of such a density necessitates ruling out the following: pneumococcal pneumonia, bronchopneumonia, acute bronchitis, tuberculosis, pulmonary abscess, acute bronchiectasis, metastatic disease, and the viral and rickettsial pneumonias of known etiology.[29]

Despite the fact that relatively few cases of mixed pneumonias have come to autopsy, the infection usually being a fairly benign one, gross and microscopic findings are well described. The distribution of the infection is lobular in the same sense as bronchopneumonia but histologi-

cally the picture is quite different in that alveolar exudate is minimal, almost acellular, and the site of the major tissue reaction is in the alveolar cells and alveolar septa. Peribronchial stromal elements are also heavily involved. The cellular exudate may vary from one mostly mononuclear, with many plasma cells, to one frankly polymorphonuclear with a fair proportion of macrophages. Phagocytic cells may contain few to many bacteria. Bronchioles are involved in a spotty manner and have pus, desquamated epithelial cells, and mucoid fluid in their lumina. Mucosal ulceration is frequent. Bronchi usually show edema, contain scanty fluid or mucoid exudates, and occasionally undergo ulceration. Squamous metaplasia of respiratory epithelium together with the presence of mitotic figures has led some to speculate on a possible relationship between this type pneumonia and pulmonary malignancy.[41, 42] Some observers have noted the presence of cytoplasmic and nuclear inclusion bodies which they feel implicate viral agents as etiological factors in the production of the disease.[43] It must be pointed out that the absence of such changes does not rule out a viral etiological role, though most reported cases do not mention such cytologic changes.

Bacteriologic studies of patients suffering from mixed pneumonias have been many. Abrahams,[32] studying respiratory infections in a British Army Command in 1917, found *Hemophilus influenzae* and pneumococci constantly in sputum samples. *Neisseria catarrhalis*, streptococci, and staphylococci were also frequently found. Sante,[44] reporting studies of American troops at the same time, found typable pneumococci, streptococci, and staphylococci in sputum samples. Others have subsequently confirmed these observations.[9] Some have noted in their series absence of *Hemophilus influenzae* and scarcity of pneumococci.[35] Longcope,[14] in 1940, stated no abnormal flora were found but that later in the disease alpha-streptococci, *Staphylococcus albus*, and a few pneumococci were found. He does not define a "normal flora." Kneeland and Smetana[15] also found no deviations from the normal respiratory flora and suggest that the presumably viral nature of the disease they describe might actually protect the patient from bacterial invasion. In 1944, the Commission for the Investigation of Respiratory Disease[8] reported comprehensively on the exact nature of the respiratory flora in acute respiratory infections. These observations are of particular value for they include studies of bronchoscopic aspirations and delineate the flora near the site of the pneumonia. Such observations are rare in the literature and, together with the established fact that the lungs are ordinarily sterile, become most significant. Parker[37] has reported a series of eight cases in which he found the same organisms at autopsy in the nasopharynx and lungs of patients who had died. Some feel that the viruses common to epidemic respiratory infections do not enhance the incidence of streptococcal infections.[45] Others have noted that, experimentally, viruses together with *Streptococcus viridans* produce a more severe pneumonitis than viruses alone.[46] Intranasal inoculation of experimental animals with nasopharyngeal washings of patients with upper

respiratory infections has produced pneumonia of interstitial type indistinguishable from that seen at post mortem in man.[47]

Finally, in 1947, Reimann[30] in his review presented a list of agents which have been associated with viral pneumonias in man:

1. Virus of Stokes
2. Mongoose virus
3. Pneumonia virus of mice (PVM)
4. Mouse pneumonia virus (Dochez)
5. Mouse pneumonia virus (Gordon)
6. Guinea pig virus
7. Cotton rat virus of Eaton (AP)
8. Virus of Rhoads
9. Virus of Johnson
10. Cat virus
11. Gray lung virus of mice

The etiology and pathogenesis of the mixed pneumonias remains today a controversial point. The chief deterrent to solution of this problem seems to be our unsatisfactory knowledge of viral behavior. The experiments of McCordock and Muckenfuss,[48] in 1933, demonstrated that vaccine virus could produce an interstitial pneumonia in the absence of bacteria and that the exudate could be made to be predominantly mononuclear or polymorphonuclear depending on whether the dose of infecting virus used was small or large, respectively. They also showed that pneumonia of lobular distribution could not be produced in the absence of bacteria in the lungs. In 1936, Cass[49] noted that the prognosis in the disease is uniformly good if the white blood count stays low but that its rise suggests a rapidly advancing disease process in the chest. Later Scadding in his discussion of lung changes in influenza expresses the opinion that those cases he observed which had signs of consolidation represented a secondary bacterial infection superimposed on a pre-existing viral infection. He suggests that the viral infection produces inflammatory edema which impairs proper drainage of the lungs thus diminishing the normal resistance to bacterial invasion. He felt that if a virus and bacteria combined in proper proportions, fulminating disease might result. He concludes that a pure virus infection can descend to any level in the lungs and there predispose the patient to secondary bacterial infection and states that viral pneumonia is rarely, if ever, fatal prior to bacterial invasion and that any combination of viral-bacterial synergism may occur.[9] Some, however, have felt their reported cases represented wholly viral infections and make no mention of bacterial flora having a role in the disease.[50, 51] In 1939, Goodpasture[43] reported five cases of viral pneumonia in children following exanthemas in which he felt there was secondary bacterial invasion of the lungs but all his cases are ones in which there was gross sepsis in debilitated patients. Reimann and Havens[35] have stated, "It should be recognized that, as in the case of influenza, both mild and severe forms may be due to the same cause without the agency of bacteria, although bacteria may eventually invade the damaged lung." Since then others have stressed the role of secondary bacterial invaders and some have not seen fatal disease in their absence.[39, 46] Smith notes the following signs as indicating secondary bacterial invasion: increased number of pathogens in the sputum, the development of bacteria, an abrupt rise in temperature or white blood cell count, and the appearance

of shaking chills. By 1947, Reimann[30] stated frankly that these pneumonias comprised a syndrome probably composed of a number of entities and were caused by many similar or dissimilar, related or unrelated agents. He added further that most workers felt that several viruses acting in a synergistic way with bacteria produced the clinical picture. More recently some workers have sought to place these pneumonias in a category which does not bear the important prognostic implications of the word "pneumonia" by calling them "infected atelectasis" or "aspiration pneumonia."[33, 40] This is pathologically unsound for atelectasis is rarely seen, the conditions are pneumonias in the pathologic sense of the word, and aspiration is the principal mechanism by which any agent enters the lungs to produce inflammation. In 1953, James[52] compared what he termed virus pneumonia and aspiration pneumonia. His differentiation is based in part on complement fixation tests for known viruses and nonspecific agglutination tests (cold agglutinins and streptococcus-MG). This does not take into consideration the ubiquity of viruses, their great variability, or the opinion today that many relatively unknown viruses produce respiratory infections. James also uses the response of the patient to chemotherapy as a means to differential diagnosis which is hardly valid if the prevailing theory of synergistic etiology is correct.

At the present time, the following conclusions regarding the mixed pneumonias seem warranted:

1. They produce a most variable syndrome usually less severe than bacterial pneumonias.

2. The syndrome has been recognized for many years but only in the past fifteen years has much about the subject appeared in the literature.

3. Pathologically the disease is a lobular pneumonia of interstitial type.

4. This syndrome is constantly associated with upper respiratory infection and represents a progression of a synergistic infection down the tracheobronchial tree.

5. Bacteria which are normally seen in the upper respiratory tract assume etiological importance when they are found in the lungs which are normally sterile. This situation is analogous to the presence of bacteria in the spinal fluid.

6. Often the disease is so mild that it is found only when chest films are taken.

7. The response to chemotherapy is variable.

Bronchiolitis.—This condition is often called capillary bronchitis, implying involvement of the smaller bronchi and bronchioles and is probably best known in recent literature as "primary virus pneumonitis (or pneumonia) of infancy" through the work of J. M. Adams. For reasons seen below in the discussion pertaining to pathology and etiology, this condition probably should be included in the section on mixed pneumonias. However, the fact that it is seen almost exclusively in infants and young children together with the common observation of severe dyspnea and rapid onset tend to establish it as a unique entity, at least in so far as its import to the patient's prognosis is concerned. It has been studied by British workers who give a description of the clinical picture identical

with that commonly seen in this country. Some, however, do not seem much impressed by the bronchiolar obstructive phase of the disease. Their autopsy studies confirm in every detail those of Adams, except for the observation of inclusion bodies in the bronchiolar epithelial cells.[53]

The clinical picture is a rather constant and characteristic one. Adams' series have consisted of newborn and young infants. The disease, however, is often seen in children 2 years of age, rarely in older children. There is a prodromal upper respiratory infection and a history of cough, sneezing, and onset of progressive dyspnea is obtained. The patient usually does not appear especially ill, often the temperature being under 100° F. rectally. The most striking aspect of the infection is the degree of dyspnea present. The patient is anxious and restless due to air hunger and may prefer to sit up. Cervical, supraclavicular, and substernal retraction is seen. Cyanosis may be present and vary in degree from slight duskiness to rather marked cyanosis and is due to the ventilatory impairment. The chest often assumes a barrel shape, with the rib cage raised anteriorly and with limited motion, a manifestation of an acute obstructive emphysema. It is hyperresonant; the inspiratory phase is shortened, the expiratory phase much prolonged, associated sometimes with medium to fine râles, and almost constantly with an expiratory wheeze.

X-ray findings in the chest film in bronchiolitis are dependent on the stage of the disease. Early in the disease the density of the lung fields is diminished because of the presence of an acute obstructive emphysema. If the disease progresses, fine patchy densities may be seen which are presumed to represent bronchiolitis and scattered secondary atelectasis. If the disease has progressed to this point, resolution of x-ray findings requires some time and clinical improvement precedes it by some days.[54]

Post-mortem examination of the lungs about the seventh day of the disease reveals grossly bronchial and bronchiolar exudates which sometimes may be quite purulent in appearance. There is also ulceration of bronchial and bronchiolar epithelium. Areas of atelectasis, hemorrhage, and edema are common. On microscopic examination a monocytic infiltrate is seen in the stroma around the bronchi and bronchioles and extends into the adjacent alveolar septa. Serous exudate may be seen in some alveoli.[53] According to Adams, the most significant finding seen microscopically is the presence of acidophilic cytoplasmic inclusion bodies about 3 to 6 μ in diameter in the respiratory epithelium. These inclusion bodies are also frequently found in smears of the pharyngeal mucosa of patients with the disease.[54, 55]

Bronchiolitis is presumed to be of purely viral etiology though no specific causative virus has been identified. Evidence for such an etiology is rather adequate, but the possibility of there being several causative viral agents has by no means been excluded. The appearance of bronchiolitis being confined almost entirely to patients with upper respiratory infections suggests strongly the participation of a viral agent in the pathogenesis of the condition. The presence of a normal nasopharyngeal flora together with animal experi-

ments in which micro-filtered human pharyngeal washings have produced a pathologic picture in the lungs the same as found in children at post mortem have led some to feel the disease has a solely viral etiology. Others, however, have noted a constant relationship between the number of inclusion bodies found and the number of bacteria present on microscopic section. The significance of this observation is not clear.[58] Adams[56] was the first to note the presence of these inclusion bodies, and found them in about 85 per cent of infected young infants, but because of the probable ubiquity of the infecting agents, interpretation of the presence of these bodies must be made with care. In 1948, he reported six cases of congenital pneumonitis in newborn infants of mothers who had upper respiratory infections and in which inclusion bodies were found in the pharyngeal mucosa.[54, 57] He feels aspiration is more important in the development of infections of the lower part of the respiratory tract than is commonly believed and points out that, in the supine infant, the trachea forms an angle downward of about 20 degrees with the horizontal and that gravity tends to augment the aspiration of infected secretions from the upper tract. With the infant on his abdomen, the angle is upward and drainage of secretions toward the mouth is implemented, and may be an explanation of why infants and young children with respiratory infections seem more comfortable prone than supine.

Finally, Adams[58] states that while it is logical to present pneumonias from a bacteriologic point of view, it is difficult to do in pediatrics because of the lack of sputum for study, the variety of predisposing illnesses, and the fact that mixed infections play an outstanding role in children's respiratory disease.

The following statements regarding the place of bronchiolitis in the classification of acute respiratory disease which is presented in this review can probably be safely made in the light of present-day knowledge of these conditions:

1. Bronchiolitis is another manifestation of the typical natural tendency for respiratory infections to move downward in the respiratory tract.

2. The etiology is probably viral, but the role of bacteria is unknown except where they may appear as secondary invaders, occasionally producing death from overwhelming bacterial bronchopneumonia.

3. The disease is characterized chiefly by obstructive dyspnea out of proportion to the systemic manifestations of the disease.

4. Etiologically and pathologically the disease should be placed in the category of what have been previously termed "mixed pneumonias" were it not for its peculiar pediatric implications.

SUMMARY AND CONCLUSIONS

1. Acute respiratory infections of the larynx, tracheobronchial tree, and lungs are discussed in reference to pathogenesis, classification, and diagnosis.

2. A classification of acute respiratory infections based on the anatomic distribution of the infection is suggested. It is felt that in most instances, the etiology of these infections involves such a mixture of eti-

ological agents, both bacterial and viral, as to preclude etiological classification in the practical sense of the word. In addition, it is the anatomic situation which most affects the patient's respiratory function. Finally, respiratory infections may usually be so classified by the clinician by means of a good history and careful physical examination.

3. Diagnostic criteria and their pathogenesis are discussed.

4. Two conditions of somewhat controversial status, the so-called "primary atypical pneumonia" and "primary virus pneumonitis of infancy" are discussed. Certain conclusions are made regarding the place of these entities in the whole spectrum of respiratory infection which seem tenable at the present time and provide a basis for rational treatment.

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Comments on Current Literature

POLIOMYELITIS: INCIDENCE OF SUBCLINICAL INFECTION DURING AN EPIDEMIC

RECENT developments in tissue culture methods and their application in the study of virus disease have made available to workers interested in the epidemiologic aspects of poliomyelitis, a valuable and efficient tool. The in vitro method for detecting the presence of poliomyelitis virus, based on the cytopathogenic effect of the virus in cultures of human or monkey tissues, serves likewise as an indicator system which can be used for demonstrating the presence of neutralizing antibodies for all three strain types: Type I (Brunhilde), Type II (Lansing), and Type III (Leon). Prior to the perfection of this in vitro method, monkeys or mice (Lansing) were required for the demonstration of neutralizing antibodies.

Utilizing these newly developed techniques, Melnick and Ledinko[1] (*American Journal of Hygiene*, September, 1953) undertook a study of the poliomyelitis epidemic which occurred in Winston-Salem, N. C., during the summer of 1948. The outbreak was characterized by the usual epidemiologic pattern in that there were a few cases in the spring, followed by a marked increase of cases in June, with peak incidence in July, continuation through August, and subsidence in the autumn months. Over the state of North Carolina the attack rate was 62 per 100,000 population, and the ratio of paralytic to nonparalytic cases was estimated to be two to one.

The purpose of this investigation as outlined by the authors included:

1. A study of the distribution of antibodies to the three strain types of virus in the juvenile population in Winston-Salem, N. C., during 1948;

2. The effect on the development of antibodies of living through an epidemic of poliomyelitis;

3. A direct determination of the ratio of subclinical infection to clinical disease.

Accordingly, blood samples were obtained from 200 healthy children during the first week of June at a time when only four cases of poliomyelitis had occurred. In November, after the epidemic had subsided, blood samples were obtained again from these same 200 children. As it happened no illnesses resembling poliomyelitis were reported in 1948 in this particular group.

The 200 children in the study were divided into two socioeconomic groups. The so-called upper class group included those who lived in single family dwellings with good sanitation, and who were not subjected to overcrowding. Classified in the lower socioeconomic group were those living in crowded run-down districts where sanitation was poor, where multiple family use of toilets or outdoor privies was common, and where general personal hygiene was not good.

Serum samples from the two groups taken before the epidemic and after its subsidence were studied for the presence of antibodies to the three strain types of poliomyelitis. The results showed that in the case of Brunhilde virus (Type I), serum specimens collected during the preepidemic period were appreciably positive for antibodies in 68 per cent of the newborn infants, in only 5 per cent of the infants in the age range 6 months to 2 years, and in 15 per cent of the children 3 to 4

years of age. In the age range 5 to 14 years, the level of positive antibody tests rose to 30 to 44 per cent. Studies on the serum samples from these same subjects taken at the end of the epidemic period showed that there had been an increase in the incidence of antibodies to Type I in all age groups, but that the increase was most marked in children under 4 years of age.

Data obtained concerning the Lansing virus (Type II) showed that antibodies to this strain were present in the majority of newborn infants, but were lost during the first year of life. Only 15 to 22 per cent of the children had antibodies to Lansing strain through the first four years. Older children had antibodies in a proportion of 40 to 46 per cent. Post-epidemic investigations indicated that all age groups had increased levels of antibody to Lansing virus, except those who were under 1 year of age. Increase in Lansing-strain antibody was most pronounced in children 1 to 3 years of age.

In the case of the Leon strain, 70 per cent of the newborn infants studied showed appreciable antibody titer. This titer seemed to have declined markedly during the first year of life, since antibody levels were low in children from 1 to 4 years of age. In the age range 5 to 6 years, titers were appreciably positive in 40 to 44 per cent, and in children of 7 to 14 years, 50 to 58 per cent gave positive result. It is interesting that for the Leon strain of virus, there was no change during the epidemic, so that the findings in serum specimens collected late in the epidemic, or after the epidemic, were essentially the same as those for specimens collected early or before the epidemic. Thus with respect to antibody levels, the results obtained were essentially similar for all three types of poliomyelitis virus, with the exception that for the Leon strain there was no evidence of increases in antibody titer during the epidemic period.

Observations concerning the presence of antibodies to more than one strain of virus were of particular interest. These authors found that in the pre-epidemic period, 41 per cent of the children in the older age group had antibodies to two or three types of poliomyelitis virus, and in the postepidemic period, 46 per cent of the older children. In the younger children, under 4 years of age, only 3 per cent had multiple antibodies in the spring, and 13 per cent in the fall.

Results concerning the levels of antibody in children of the two socioeconomic groups were interesting. When the figures were analyzed, it was evident that antibodies to all three types of virus were present to a significantly higher degree in the blood of children belonging to the lower income group. This higher incidence was apparent in the results obtained both in the spring and in the fall. As the authors point out, it is noteworthy that similar observations have been made concerning the presence of antistreptolysin "O" and gamma globulin levels.[2]

The probable infection rates during the epidemic, as determined by anti-

INFECTION RATES* IN UPPER AND LOWER SOCIOECONOMIC GROUPS OF WINSTON-SALEM DURING SUMMER OF 1948

	UPPER	LOWER
Type I poliomyelitis virus	7	45
Type II poliomyelitis virus	14	26
Type III poliomyelitis virus	0	0
High Point Coxsackie virus (a local strain)	46	33
Streptococcus	0	0
Influenza virus	0	0
Mumps virus	4	2

*$\frac{\text{No. developing antibodies during epidemic period}}{\text{No. without antibodies in pre-epidemic period}} \times 100$

body studies in the two socioeconomic groups, are summarized in the accompanying table.

Over-all analysis of the data obtained from these studies led the authors to conclude that the number of cases of inapparent infection per clinical case was of the order of 175 for infants under 1 year, 100 for infants 1 to 2 years of age, 73 in children 3 to 4 years of age, 62 for children 5 to 9 years of age, and 95 for those 10 to 14 years of age. Expressing the results as ratio of subclinical infection to paralytic cases of poliomyelitis, the authors state that there were 6 to 16 frank cases of the disease per 1,000 inapparent infections, with the lowest incidence of the paralytic form of the disease in infants, and the highest in children from 5 to 9 years of age.

The authors compare their ratio of inapparent or subclinical infections with estimates made previously. For example, in a New York City study, based on the amount of poliomyelitis virus recovered from ample sewage sampling during an endemic period of low disease incidence, the estimate was one in 1,000[3]; from a family-to-family survey of the history of poliomyelitis in large groups of people, the estimate was 10 to 1,000[4]; and the ratio arrived at by Howe[5] from a comparison of the reported cases of obvious diseases with those of poliomyelitis during the same period was 5 to 1,000.

Studies such as these in which objective information is accumulated under well-controlled conditions will result inevitably in a better understanding of the natural history of infantile paralysis. The development of new and efficient laboratory tools will be of great importance in carrying out such investigations.

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News and Notes

Dr. Richard L. Day, Associate Professor of Pediatrics at Columbia College of Physicians and Surgeons, has been appointed Professor of Pediatrics at the State University of New York College of Medicine at Brooklyn on a full-time basis. Dr. Charles Weymuller who has been Chairman of the department on a part-time basis since 1936 will continue as Professor on a part-time basis. Dr. Day will assume his new duties December 1.

Dr. Heyworth N. Sanford, who has served as acting head of the Department of Pediatrics at the University of Illinois College of Medicine since September, 1952, has been appointed as head of the department. Dr. Sanford has been a member of the faculty of the University of Illinois since 1941 when he was appointed clinical associate professor of pediatrics. He was promoted to full professor in 1944. He has resigned positions as chairman of the Department of Pediatrics at Presbyterian Hospital but will continue his association with Cook County Hospital.

Dr. and Mrs. Charles Hendee Smith celebrated their 50th wedding anniversary on September 8. Dr. Smith retired as Professor of Pediatrics at New York University in 1942 and has since engaged in active pediatric practice in New Brunswick, N. J.

The theme for the annual postgraduate pediatric "refresher week" at **Tulane University** Feb. 8 to 13, 1954, will be "Surgery for Infants and Children." The program will be under the direction of Dr. Ralph V. Platou and Dr. Alton Ochsner with Dr. Willis Potts and Dr. Thomas Baffes as guest speakers. Major emphasis will be given to consideration of medical and emotional preparations and aftercare, choice, and conduct of anesthesia, diagnostic procedures, and recent advances in related fields. Those interested should apply to: Director, Division of Graduate Medicine, 1430 Tulane Ave., New Orleans 12, La. Registration, as usual, is limited to forty qualified specialists.

At the annual postgraduate conference in pediatrics held at the **State University of Iowa,** Sept. 16 and 17, 1953, in conjunction with the fall meeting of the state Pediatric Society, one session was devoted to a memorial program honoring Dr. Jeans. At this session the **Philip Charles Jeans Pediatric Library,** State University of Iowa, was dedicated. Speakers were Dr. Jean V. Cooke, Professor Emeritus, Department of Pediatrics, Washington University, St. Louis; Dr. L. A. Maynard, Professor and Head of the School of Nutrition, Cornell University, Ithaca, and Chairman of the Food and Nutrition Board of the National Research Council; Dr. James R. Wilson, Secretary of the Council on Foods and Nutrition, American Medical Association. Particular emphasis was given to Dr. Jeans' long service and many contributions as a member of national advisory boards, for this phase of his professional life was less familiar to physicians of the state. The dedication followed the talks. Dr. Lee Forrest Hill of Des Moines read a eulogy of Dr. Jeans. The library was then dedicated to Dr. Jeans by Dr. Charles D. May, Professor and Head of Pediatrics, State University of Iowa. The dedicatory plaque reads as follows: "This library is dedicated in appreciation of Philip Charles Jeans, M.D., Professor and Head, Department of Pediatrics 1924-1952. A wise clinician, thorough investigator, humble teacher, and understanding friend."

The **First Congress of the South African Pediatric Association** met in Durban, Aug. 20 to 22, 1953, Dr. Seymour Heyman of Johannesburg presiding. The society has some thirty-two members of whom seventeen were present. In addition, several associate members (physicians who devote their time to child care but who have not had the required training for qualification) and a number of guests attended. Among the guests were Dr. Hugh Taylor of New York, Director of McCord Hospital in Durban, and Drs. Harry and Ruth Bakwin also of New York.

Book Reviews

Sexual Behavior in the Human Female. Alfred C. Kinsey, W. B. Pomeroy, C. E. Martin, and P. H. Gebhard, Philadelphia, 1953, W. B. Saunders Company, 842 pages. Price $8.00.

Some five years ago in reviewing *Sexual Behavior in the Human Male* it was noted that this was the first of eight projected studies from the Institute for Sex Research at Indiana University headed by Dr. Kinsey. The second, a companion text, *Sexual Behavior in the Human Female* has now been published. The "Male" book received for review was one of a first edition of 5,000 copies. The "Female" first edition we have read is one of 250,000 copies—a figure the "Male" finally reached. We have often wondered how much the vast majority of purchasers and readers of the "Male" really got out of it. Little we imagine in the factual tabular data presented that they expected. As stated editorially in the JOURNAL at that time, the book would have repercussions far beyond the field of medicine, although brought out by a medical publisher. The same holds true for the "Female" text which, except for the chapters on neural mechanisms and hormonal factors in sexual response, is of sociological importance rather than medical.

Dr. Kinsey and his associates used the same techniques in collecting data for this volume as used for the previous one. Considerable space is given to the method of sampling, as it was the distribution of the sample which was one of the chief points of attack as to the material's presenting a fair or scientific picture of male sexual behavior. Dr. Kinsey considers his method as the only reliable method of sampling with the techniques he uses, which involves a personal catharsis to the interviewer. He frankly points out certain specific gaps in the distribution. The chief fault in this respect would seem to be a higher percentage of the well-educated groups than is found in the general distribution of females. We doubt, however, if this is of great importance in the general picture reflected by the data.

The chief findings have been so widely discussed and publicized in numerous articles in the lay press, based on prepublication conferences with journalists and reporters in a ballyhoo unprecedented in the book publishing world, it seems superfluous to repeat them in detail. To the pediatrician the findings and discussions relating to sex education are the chief matter of interest. As a matter of fact it was an attempt to find an answer to this involved question that started Dr. Kinsey on his studies of human sexual behavior. The data in this and the previous book show that many children acquire knowledge of sexual phenomena in very early childhood, and nearly all from other children. This simply lends support to a well-known and accepted fact, and data in the form of types and percentages add little to what is already known. Perhaps the most important statement on the subject in the text is that whether sex information, so far as it is related to its impact on the future sex life of the individual, is better when obtained from adults or from other children, is a question the author feels cannot be answered from the data. Early attitudes he considers as being very important upon the future sex life of the individual, which is also not a new idea but one generally accepted by physicians. We will all agree with Dr. Kinsey that sex education is important, but that what children should be taught, at what age they should be taught, who should teach them, and how they should be taught are matters of theory and opinion. It is to be sincerely hoped that out of the studies of the Sex Institute some useful information will eventually be obtained, as it is an important subject about which much drool and drivel has been written and spoken by enthusiastic crusaders who at times have harmed more than they have helped. Dr. Kinsey and his associates are to be praised for their efforts to put sex education on a sound rational basis, even if they have so far been unsuccessful.

B. S. V.

Advances in Pediatrics. Edited by S. Z. Levine, M.D., Chicago, 1953, The Year Book Publishers, Inc., vol. 6, 323 pages. Price $7.50.

The 1953 volume of *Advances* holds more of interest to the practicing pediatrician than some of the previous volumes. There are seven reviews or discussions. One of the most interesting by Ingalls of the Harvard School of Public Health entitled *Preventive Prenatal Pediatrics* is a discussion of the factors leading to fetal death and congenital malformations and their prevention. He feels that congenital malformations are for the most part preventable, and outlines the scope of studies and investigations which are needed in the field. Among the other discussions are *Lymphosarcoma* by Dargeon, *The Lipoidoses* by van Crevald, *Pulmonary Pathology in the New Born* by Edith Potter, and *Megaloblastic Anemia of Infancy* by Zuelzer and Rutzky.

American Pediatric Directory. Ed. 6, 1953-1954, Knoxville, Tenn. Joe T. Smith, M.D. Price $10.00.

The Sixth Pediatric Directory edited and published by Dr. Smith contains the names, grouped geographically and alphabetically, of the pediatricians in the United States and Canada. Dr. Smith lists 3,898 as certified by the American Board of Pediatrics, 1,928 who give full time to pediatrics but are not certified, and 2,287 part-time pediatricians or general practitioners majoring in pediatrics.

Handbook of Orthopaedic Surgery. Alfred Rives Shands, Jr., St. Louis, 1952, The C. V. Mosby Company, 644 pages. Price $8.00.

The fourth edition of the *Handbook of Orthopaedic Surgery* by A. R. Shands is a revision of the previous editions of this excellent book. Recent knowledge has been added and illustrations have been changed and increased in number. However, the book remains a "handbook," with clear simple description of orthopedic conditions and brief outline of the major types of treatment of these conditions.

For simplicity, subject matter is discussed under the headings of congenital abnormalities, affections of growing and adult bone, infections, arthritis, neuromuscular disabilities, tumors, and fracture deformities. Trauma is limited to the deformities resulting from trauma. Those conditions which do not fall into above general categories are discussed under the regions or joints that are involved. Bibliography is lengthy and complete.

This is an excellent book for the student or the practitioner who needs information about diagnosis and treatment of orthopedic disabilities without extensive detailed description.

D. ELLIOTT O'REILLY

Nutritional Studies in Adolescent Girls and Their Relation to Tuberculosis. Joseph A. Johnston, M.D., Springfield, Ill., 1953, Charles C Thomas, 120 pages. Price $7.50.

In this monograph Johnston summarizes the careful and painstaking metabolic studies he has been carrying on for the last twenty years in the field of adolescence, with particular reference to the relation between nutritional status and tuberculosis. His thesis is that the increase in tuberculosis found in adolescent girls may be due to a failure to meet the nutritional requirements peculiar to the growth that takes place at this time, and further that the disease may be influenced by the adequacy of the diet to replenish deficits. As a measure of nutritional status and growth processes Johnston uses long-term nitrogen and calcium balances. Many parts of the study brought together in the monograph have been presented previously. Johnston feels his work seems to show a correlation between an adequate nitrogen storage and the course of the infection, although the latter is influenced by many other factors. Aside from the relationship of the studies to tuberculosis the material and work adds much to our basic knowledge of the metabolic changes which take place during adolescence. The material is excellently and clearly presented and the volume is illustrated with many graphs and roentgenograms.

Editor's Column

OVER THE EDITOR'S DESK

MANY letters come to the Editor's desk. An occasional type is from someone who has an idea or theory he wishes publicized. We recall a number with some theory as to the cause and spread of polio and all without factual support. The Editor has been reviled, and even called a "coward," because of his refusal to give publicity to the unsupported theory.

* * * *

Another more frequent type is from someone who is perplexed by "contradictory statements" which have appeared in the JOURNAL. A recent example was a letter which stated that the men at his hospital were confused over the statement of Dr. Karelitz, of New York, in his review of the antibiotics in the April issue, recommending the routine use of antibiotics when the diagnosis of measles is made in a young child, and that of Dr. Shaw, of San Francisco, in an editorial in the August issue, who considers this use as "frivolous." The question is simply whether the advantages to be gained by the prophylactic use of the antibiotics in measles outweigh the disadvantages, or vice versa. In this particular example a definite difference of opinion exists between two men with vast experience in the handling of communicable diseases, and each is expressing his honest opinion. Owing to the differences in the severity of measles epidemics and the time of the year in which they occur in different localities, it would be difficult to conduct controlled studies which would be of comparative value. Hence whether or not antibiotics should be used routinely for prophylactic purposes is a matter of opinion.

In connection with the Editorial we quote a letter to Dr. Shaw from Dr. Phillip Rothman, of Beverly Hills.

August 10, 1953.

Dear Dr. Shaw:

I have just read your editorial on "The Frivolous Use of Antibiotics" and heartily agree with all your statements. May I add a few comments. There seems to be very good evidence that little or nothing can be accomplished as far as the men in practice are concerned. It seems to me that the only possible way of improving the situation is by prophylaxis, so to speak, in the education of medical students and internes. As long as the abuse of antibiotics is so prevalent in all hospitals, including teaching institutions, any improvement in their use is doubtful. The recent report by Karelitz is a very fair cross section of what is going on everywhere. In a 24 hour survey of the use of antibiotics in the pediatric service at Mount Sinai Hospital only 22 of 45 patients received correctly chosen drugs in suitable dosage. That the assistant residents, senior residents, and attending physicians permit this to occur is the basic cause of our difficulties and it exists as far as I know in the best institutions.

This matter of "contradictory statements" involves a fundamental question of editorial policy. It is not and should not be the function of the Editorial Board to take a stand on matters of opinion to the extent that a contrary opinion is excluded. Rather the Editorial Board considers it a function of the JOURNAL to present differences of opinion held by men of the standing and experience of Dr. Karelitz and Dr. Shaw. We realize it may be confusing to some of our

readers, particularly the younger men who are in the "hangover period" of their medical school days and are still looking for the definite authoritative statement. Those with a longer experience realize how often the truth of today is the error of tomorrow, and the error of today is the truth of tomorrow. So as a matter of editorial policy the readers of the JOURNAL will now and then continue to find contradictory statements.

* * * *

A thing we have never been able to fathom is why certain articles or editorials bring comment and why others do not. A communication some time ago on the subject of early institutionalization of the mentally retarded child aroused considerable discussion among the members of the Board, and finally led to an editorial expressing the viewpoint of five members. It is an important practical debatable question and we expected it to arouse considerable discussion. Nary a word was received adding to the discussion. On the other hand, a recent editorial on the relatively unimportant subject of snake bite, whose purpose was to point out that it was to a large extent a pediatric emergency, brought a lot of comment—even from Europe—on snakes and methods of treatment. It was quite a surprise.

* * * *

Recently in the mail there have been two letters commenting on JOURNAL articles, which we feel might interest our readers. The first refers to the article on "The Comics," by Dr. Ruth Bakwin in the May issue, and the editorial the following month. The writer takes issue with Dr. Bakwin and the Editor on the degree of harmfulness of the Comics—again a matter of opinion.

New York
August 19, 1953

Dear Dr. Veeder:

It was with some interest that I first read Dr. Ruth Bakwin's discussion of the comics in the May issue of the JOURNAL. However your editorial comments in the June issue of the JOURNAL served to precipitate a growing concern on my part on this subject and prompts me to write this letter.

Contained within your comments are several assumptions which are difficult to validate. You state, "History, Biblical stories, current events, modern science, and favorite stories are now the chief substance of the comics." Perusal of the comic book shelf of any local store will demonstrate that a majority of the comics are ghastly collections of murder, mayhem, sadism, weird adventures, crime and brutality. A 1951 analysis of ninety-two comic books reported the following content: 216 major crimes; 86 sadistic acts; 309 minor crimes; 287 incidents of anti-social behavior; 186 instances of vulgar behavior; 522 physical assaults; and the technique of fourteen murders in detail.

The content of one comic book, the June-July 1952 issue of *Crime Suspense Stories* might serve as a particularly appropriate illustration. It portrays a professor at a medical school murdering his wife, multilating her body to prevent identification and then hanging the body among the corpses kept at the school laboratory for purposes of dissection by his students. The drawing which graphically depicted the professor strangling his wife, bore this caption:

> How long we struggled I don't know —but an ominous silence seemed to clear my senses! Her body was completely limp and her eyes bulged from their sockets from the pressure of my fingers that were knotted around her neck! . . . A few quick slashes with a kitchen knife entirely obliterated her features! Then after pulling her teeth and removing her jewelry and clothing my wife was completely unrecognizable.

Then there is the question of "the psychological value of the comics for the child, as satisfactions, as identification with the hero of the text, as an outlet for aggressive-

ness, and because of their cheapness they can be bought *without* adult assistance and thus give a freedom of choice of value to the child.'' I cannot imagine what satisfaction a child might obtain from the multitude of comic books dealing with crime, sex, corruption, war, which by far outnumber those taking their stories from the Bible and other literary classics. Even the animal comics contain the same elements of violent plot structure.

As for identification with the hero of the text, I seriously question the psychological value of this mechanism, when the hero is a superman who defies both the laws of nature and man by taking the law into his own hands. They unfortunately personify the theme of ''Might makes Right'' more than they do ''Good always triumphed over Evil.'' A frequent comic book character is the long-haired crackpot or scientist as a white-gowned madman plotting to destroy the world—a fitting tribute to the personal industry and character of our scientists.

As an outlet for aggressiveness, some of the reported events of the past few years would suggest that comic books have served as a stimulus rather than an outlet for aggressiveness. There have been specific incidents of a kidnapping plot, murder and poisoning committed by children following the precise pattern outlined in comic books.

As to the freedom of choice of value to the child, there must be positive values offered in choice. Recognizing this, in many parts of Canada and in some European countries such as Sweden, the sale of comic books dealing with crime, violence and sex is forbidden by law.

Because no one can deny the great value of the comic as an educational medium, it is extremely important that we, as physicians, who work with children explore and evaluate this subject completely and carefully. The mere recognition of its educational value is evidence of its importance in the lives of our children. It is gross oversimplification to describe the phenomenon of comic books as an aspect of history repeating itself. Just as it is gross oversimplification to ascribe the growth of juvenile delinquency and violent crimes by young Americans to the influence of comic books. Their impact on American children has to be evaluated as part of our entire cultural pattern within the over-all atmosphere of war tensions, crime, corruption, cynicism, and resort to force. The ultimate mental health of our children necessitates our considered, honest, and scientific appraisal of this and other aspects of our culture.

Sincerely yours,
SOL NICHTERN, M.D.

To any who might feel as Dr. Nictern we recommend reading an essay by the late G. K. Chesterton, *A Defense of Penny Dreadfuls.* We quote: ''It is the custom, particularly among magistrates, to attribute half the crimes of the Metropolis to cheap novelettes. . . . The objection rests upon the theory that the tone of the mass of boys' novelettes is criminal and degraded, appealing to low cupidity and low cruelty. This is the magisterial theory, and this is rubbish.''

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A second letter was a discussion of a recent ''Comment on Current Literature'' by Dr. Blattner.

August 11, 1953.

Dear Doctor Veeder:

Dr. Blattner's column in the JOURNAL, ''Comments on Current Literature'' is always interesting and instructive, and his latest one, ''Smallpox Vaccination and Pregnancy,'' in the August number is no exception. However, it appears to me that it is one sided. Dr. Blattner discusses at length Patrick MacArthur's article in the *Lancet*[1] and notes his conclusion that vaccination of a pregnant woman in the first trimester of pregnancy significantly increases fetal mortality. He makes no mention of investigations that conclude that there is no effect on the fetus. This is particularly surprising since Dr. MacArthur devotes considerable space in his article to the study by my colleagues and myself,[2] and tries to find flaws in our method of study.

Dr. MacArthur's main objection to our study is that it was retrospective whereas, his was prospective. This is not true. Neither his study nor ours was truly prospective or retrospective. A prospective study would be one in which one started with a pregnant woman who was vaccinated and followed her

right through her pregnancy and delivery. Neither of us did that. A retrospective study would be one in which one started with the dead or defective infant and went back to inquire about the mother's vaccination status during her pregnancy. Neither of us was guilty of this offense. Both of us started with the mother of the infant, but our selection of cases was different. Dr. MacArthur took the first 5,000 names of married women under 45 and wrote to them to find out whether they had been successfully vaccinated, whether they were pregnant at the time of vaccination and what the result of the pregnancy was. We obtained similar data from all women who brought their children to health stations in a specified period of time, and in 11 maternity hospitals in New York City. Our data were checked for accuracy, whereas his were not.

There are elements of bias in both studies. Ours suffers from the following:

1. A larger percentage of the mothers came from lower income than from higher income groups. It is doubtful if this factor was of importance. The results were no different in the hospitals catering to the middle class than in the city hospitals. Furthermore, animal experiments indicate that lack of certain nutritional elements may precipitate congenital deformities or a nonviable fetus. This is more apt to happen in poor than in well-to-do families.
2. No information was obtained on abortions. Such histories are not reliable. We studied the incidence of stillbirths in 1946 and 1947. Since more than ¾ of the population was vaccinated in 1947, an increase in abortions should have showed up in that year. There was no difference in incidence. (In N.Y. City a stillbirth is defined as any product of conception except a live birth).

Dr. MacArthur's study also has elements of bias:

1. There were not approximately equal numbers of women in each trimester of pregnancy. Dr. MacArthur gives reasons why he thinks this is not important.
2. Information was obtained by questionnnaire. Reliance on the success of vaccination was placed entirely on the statement of the vaccinated woman. No objective examination of the vaccinated site was made by a physician as was done in our study.
3. Information on miscarriages and abortions was obtained from the women and was not checked, nor was there knowledge whether the abortion was spontaneous or induced. Nor were checks made on the normality or abnormality of the infants born.
4. There were no controls, as in our study. The comparisons were made with a group assumed to be similar to the one studied. Dr. MacArthur goes to considerable pains to argue the latter point.

Dr. MacArthur states that in our study half the women vaccinated were retained in the study although they had no vaccination scar. He neglects to state that these women had an immune reaction and that in all our tables we compared the controls with the group that had a scar as well as with the total group. In both comparisons no statistical difference was found.

Finally, it is pertinent to point out that in a study from Sloane and Babies' Hospitals[3] carried on concurrently with ours, which was truly prospective, the conclusions reached were the same as ours. In this study the women were followed from the antepartum clinic right through to delivery. The data on abortions, deaths and malformations were reliable, since the women were seen regularly. Yet the authors conclude that smallpox vaccination during pregnancy does not increase the incidence of congenital malformations, stillbirths or infant deaths.

Yours truly,

MORRIS GREENBERG, M.D.,
Director, Bureau of Preventable Diseases,
Dept. of Health, Attending Pediatrician,
Beth David Hospital, New York City.

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Dancis, J.: The Effect of Smallpox Vaccination During Pregnancy on the Incidence of Congenital Malformations, Pediatrics 3: 456, 1949.
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Dr. Greenberg's letter was referred to Dr. Blattner who commented as follows, pointing out that it was not an editorial or review of the subject, but simply a comment on an article in the current literature:

Dr. Greenberg's letter concerning the Current Comment on smallpox vaccination in pregnancy brings into focus significant differences of opinion which were not sufficiently well-emphasized in the Current Comment in question. The divergent views expressed by these two groups of investigators are interesting, and may well be the means of stimulating more general interest in this important subject.

During the past six years, the comments on current literature have been written with a view to drawing the attention of the practicing physician to pertinent contributions in general medical literature. It has been the intention that these brief summaries should serve to acquaint the physician with new and possibly significant information, and that, if sufficient interest is aroused, study of the original articles might be encouraged. It is not the purpose of the Comments to review completely or exhaustively any one subject, nor to pass judgment on the merits of the subject-matter reviewed. It has been the hope therefore that this commentary appearing each month be accepted for what it is—a comment on current literature.